PHARMACOLOGY
CLINICAL AND EXPERIMENTAL

A GROUNDWORK OF MEDICAL TREATMENT, BEING A TEXT-BOOK FOR STUDENTS AND PHYSICIANS

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PROFESSORS OF PHARMACOLOGY

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AUTHORS' PREFACE

EXPERIMENTAL pharmacology in its widest significance deals with the reaction of living organisms to various chemical agents or, otherwise expressed, with their behavior under chemically altered conditions of life. Consequently pharmacology is to be looked upon simply as one portion of biology.

Among the endless number of possible pharmacological reactions, those possess a special interest, the study of which should aid the physician in practicing his healing art. This portion of pharmacology, "scientific drug therapy" in a more restricted sense, forms the theoretical basis of drug treatment. If it is to serve its full usefulness in explaining the ways and means by which pathological conditions may be influenced by drugs, it must constantly keep in closest relations with general pathology, *i.e.*, the study of the various disturbances which occur in disease. These two sciences working together must endeavor to explain how pathologically disturbed functions of the different organs may be influenced by drugs and be brought back to the norm. Here lies their significance for clinical teaching and medical practice.

Scientific drug therapy, as presented by us, consequently is dealt with, in so far as possible, in connection with the physician's point of view as to the seat and cause of pathological conditions. For this reason we have divided the drugs into two classes, organotropic (those influencing organs or their functions), and etiotropic (those acting on the causative agents of disease), and have thought it best to describe and analyze the organotropic pharmacological actions separately for each organ or functional system.

It appears to us not at all disadvantageous that this method of presentation requires that we frequently must hark back to a consideration of physiological basic principles, for in view of the fact that physiology has been displaced from among the final subjects in the examinations for license, it becomes more important than ever that experimental pharmacology should refresh and keep alive the knowledge of physiology in the consciousness of the candidate for license.

On the other hand, this necessitates the omission from this work of all notice of a number of pharmacological facts, which, while they

possess value for the science of pharmacology, do not appear at present to be available as material for building the foundation of a scientific therapy.

While the different chapters, as shown in the table of contents, have been written by one or the other of us, still there has been a constant coöperation and collaboration between us, which leads us to hope that we have prepared for the reader a homogeneous work.

H. MEYER,
R. GOTTLIEB.

TRANSLATOR'S PREFACE

It has been the translator's aim to present a faithful rendition into English of the original work, and if in seeking to do this he has occasionally or frequently built up sentences which are unwieldy or un-English, he hopes that this will be borne in mind as extenuation therefor. Occasionally, where he has thought it would be of value, he has interpolated comments or additions, which are regularly indicated in the text.

J. T. H.

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CHAPTER I

PHARMACOLOGY OF THE MOTOR NERVE-ENDINGS

While all parts of the nervous system may be influenced by drugs, the nerve-endings and the nerve-centres are much more susceptible to such action than are the conducting paths. This is due partly to the scanty blood supply of the nerve-trunks, but chiefly to the fact that the medullated nerve-fibres are enclosed in sheaths and are thus protected from the action of the drugs, while the nerve-endings are not thus protected and are therefore more readily affected. However, this protection is not absolute, for, when exposed nerve-trunks are moistened with solutions of drugs or exposed to volatile gases, such as ether, choloroform, etc., which are soluble in the lipoids of the medullary portion of the nerve, stimulating or depressing actions result (*Joteyko u. Stephanowska, Sowton* and *Waller*).

DEPRESSION OF MOTOR NERVE-ENDINGS

Practically, however, pharmacological action on nerve-trunks is of importance only when a concentrated solution of a drug is applied to, or in the immediate neighborhood of, a nerve, as, for example, when cocaine is purposely so injected, or when a hypodermic of ether chances to reach a nerve-trunk, in which latter case most undesirable harmful effects may result.

After discussion of the pharmacology of the motor nerve-endings, that of the central nervous system, of the sensory nerve-endings, and finally that of the vegetative nervous system will be taken up in the order named.

Curare and its readily analyzed actions form a good starting-point for the study of the pharmacology of the motor nerve-endings. Although little or not at all used in therapeutics, it should be useful as illustrating certain general conceptions of pharmacological action.

The South American arrow-poison, curare (woorari, urari), is obtained from various poisonous plants of the family of Loganiaceæ. Different explorers, notably Humboldt (1799–1804), have told how the Indians prepared this substance by evaporating aqueous extracts of various plants, often adding to it all kinds of other substances.

They also reported the enormous activity of the freshly prepared poison when it is introduced into wounds of men and animals.

Humboldt also noted that the flesh of animals thus poisoned could be eaten with impunity, and that wounds poisoned by curare could without danger be cleansed by sucking out the poison. Both of these observations indicated that when administered by the stomach it, as a rule, was inert.

Active Principles.—When brought to Europe, this poison immediately greatly interested physiologists, but, owing to the fact that its active principles readily undergo changes resulting in a diminution of their activity, it also proved far less powerful than the fresh curare.

The physiological activity of curare obtained from different sources has been found to differ not only quantitatively but also qualitatively. *Böhm*[1] showed that different alkaloids are contained in varying proportions in the three chief commercial varieties, tube curare, pot curare, and gourd curare, thus variously named from the different containers in which they are marketed. These alkaloids belong to two groups, the curines, possessing little or no true curare action, and the curarines, which produce the typical effects. The curine from tube curare is a cardiac depressant, and as, unfortunately, most of the commercial curare is of this variety, its unsatisfactory action is readily understood.

Curarine has not yet been obtained in crystalline form. Of the purest thus far prepared (*Böhm*[1]) 1/100–1/50 of a milligram produces typical paralysis in a frog. On the other hand, the curines, being heart poisons, do not produce true or typical curare effects but cause chiefly other disturbing effects. The more curarine and the less curine a curare contains, the more typical and uncomplicated by other effects is its action.

When an effective dose of curare is injected into a frog, it soon drops its head, abandons its normal crouching position, and lies on its belly. At first, irritation causes a powerful muscular response, but soon the movements become weaker. The frog no longer jumps, and the respiratory movements of the throat muscles are the only movements observed after irritation. Finally, the frog becomes entirely motionless and no reflex movements result from even the strongest stimuli. The frog, however, is not dead, for the heart continues to beat strongly. It is simply suffering from motor paralysis and, as the muscles still react readily to a direct stimulation, the cause of the paralysis must lie in some portion of the nervous system.

Analysis of the Actions.—In the middle of the last century, *Claude Bernard*[1] and *Kölliker*[1] both correctly analyzed these effects and determined that the paralysis was of peripheral causation. By ligature of the iliac artery or by tightly binding the whole of the upper thigh, exclusive of the sciatic nerve, one hind leg of a frog may be cut out from the circulation and the blood will no longer reach the periphery in this limb, although its innervation is not disturbed. If curare be injected into a frog so prepared, the rest of the frog soon becomes completely paralyzed, but movements occur spontaneously in this "isolated" leg and reflexly when the skin of any part of the body is irritated. Stimulation of the cord or of the exposed sciatic nerve causes muscular contractions in this leg but not in the other. It is thus shown that the poison does not act on the central nervous system, but must produce its effects by acting

on the nerves in the periphery. That this action is not on the nerve-trunks is proved by the fact that even after a nerve-trunk has lain for some time in a curare solution its conductivity is not impaired. It must, therefore, be concluded that the drug paralyzes the motor nerve-endings of voluntary muscles and does not produce any action on other organs.

It is of interest that *Fontana* (1781) barely failed to recognize that the action of curare was one on the motor nerve-endings. However, as at that time the existence of nerve-endings had not been realized by physiologists, after considering the hypothesis that this drug acted on the lowest portion of the motor nerves, he discarded it and located the curare action in the blood.

The sensory nerve-endings and the sensory nerve-paths are not affected by curare, for, as mentioned above, in this experiment with the "isolated" leg, irritation of any part of the body which had been exposed to the action of the drug causes reflex movements in the "isolated" leg, which could occur only if the sensory nerve-endings, nerve-trunks, and the sensory tracts and the reflex mechanism in the cord were still functionally intact.

The curare action, therefore, is limited to the motor end-organs, and the motor conduction paths remain, certainly for a time, capable of functioning.

During the first few hours of the action of curare, that the very delicate intermuscular nerve-fibrils do not lose their power of conduction, was shown by *Kühne*[1] in ingenious experiments. He succeeded in separating a muscle into two functionally independent parts and in curarizing the upper portion while the lower portion was protected by a tightly bound ligature. As, before entering the muscle, the nerve-trunk divided, sending branches to supply the two portions of the muscle, if the law of "conduction of impulses in both directions" holds good under these conditions, it should be possible for a stimulation of the nerve-fibres starting in the poisoned part of the muscle to pass up these fibres to the parent trunk and thence down the branch leading to the unpoisoned part of the muscle and to cause contraction of this part. As a matter of fact, in these experiments stimulation of the intramuscular filaments of the nerve in the poisoned half promptly and regularly caused contraction in the unpoisoned muscle. (Fig. 1.)

The motor conduction paths are affected only after long-continued exposure to curare solutions (*Kühne*,[1] *Herzen, v. Bezold*), but this is of absolutely no importance except in the frog.

It thus appears that curare interposes to centrifugal impulses a resistance at a point between the motor nerve-fibres and their final terminal organs in the muscles, a resistance which cannot be overcome if the curare action be fully developed. During the early stages of the action, this growing resistance manifests itself by a progressive tendency to fatigue of the motor nerve-endings, so that under rhythmic stimulation the contractions grow shorter and shorter (*Böhm*,[2] *Santesson*[1]).

FIG. 1.—*L*, upper part of the M. gracilis curarized; *K*, lower part not curarized.

As is to be expected the results of the paralysis caused by curare differ materially in frogs and in warm-blooded animals. Curarized frogs can continue to live for days, for, even after all respiratory movements have ceased, the respiration through the skin can supply all the oxygen necessary for their metabolism. A satisfactory circulatory function is maintained and renal secretion continues and attends to the elimination of the poison. Curare poisoning may, therefore, be caused in a second frog by injecting the urine of a curarized one (*Jakabházy*).

Only much larger doses (30 times that necessary to cause paralysis) are fatal in frogs, these larger doses interfering with the circulation and thus preventing the secretion of the urine and the elimination of the poison. *Tillie* observed recovery from a paralysis which had been induced by smaller doses and had lasted 25 days.

In mammals the results of this primary action of curare are quite different, for in them the muscular paralysis causes asphyxia and death unless artificial respiration is instituted. However, the respiratory muscles are the last to be affected, so that, by administering the proper dose, it is possible to keep a rabbit alive for hours with all its muscles paralyzed except the diaphragm.

If artificial respiration is maintained and the curare be of good quality, both heart and vessels are entirely unaffected by any but very large doses, and, as the poison is excreted through the kidneys fairly rapidly, mammals too may recover after the paralysis passes off. Only after larger doses are other functions than those of the motor nerve-endings affected. Very large doses lower the blood-pressure by a depressing action on the peripheral vasoconstrictor mechanism (*Tillie*). When this action is fully developed, neither stimulation of the sciatic nor asphyxiation causes a rise in the blood-pressure. Large doses also weaken the cardio-inhibitory action of the vagus, but the motor mechanism of the heart is unaffected. The motor nerve-endings of smooth muscle are also but little affected (*Bidder*), the intestine remaining excitable and peristalsis continuing even after extremely large doses.

In connection with its use in physiological experiments, the question as to the nature of the action of curare on the central nervous system is of great interest. In Steiner's experiments with fishes, a narcosis of the cerebrum was apparently induced, but it is doubtful if the cerebrum of higher animals is appreciably affected by curare. The spinal cord is certainly not depressed. On the contrary, according to *Tillie,* larger doses cause an increase in its reflex excitability similar to that caused by strychnine. In mammals an increase in the excitability of the vasomotor centre occurs quite early (*Sollmann* and *Pilcher*).

The effects of curarization on the temperature and metabolism (*O. Frank u. F. Voit*) are to be considered simply as a result of the abolition of the

activity of all voluntary muscles. Glycosuria, which has been observed both in animals and in man after injections of curare, is an inconstant phenomenon depending on unknown causes (*Morishima*).

It has long been known that curare administered orally is entirely ineffective, even when given in doses much larger than those which are lethal when given hypodermically. Formerly this lack of action when the drug was thus administered was explained by the assumption that the acid gastric juice destroyed or changed the curare. Although the acid of the gastric juice has a deleterious action on the easily decomposed curarin (*N. Zuntz*), this is not pronounced enough to explain the great difference between the action of the drug when given by mouth and when injected subcutaneously. Nor is it due to its not being absorbed from the alimentary canal. *Bernard*[2] and *Hermann* both showed that the comparatively slow absorption from the alimentary canal and the comparatively rapid excretion by the kidneys account for the lack of action when the drug is administered orally, for, if the renal arteries be ligatured and the drug then introduced into the stomach, typical curare effects develop.

GENERAL FACTORS AND PRINCIPLES INVOLVED IN THE PHARMACOLOGICAL ACTION OF POISONS AND DRUGS

Before going farther, it seems advisable to bring forward certain general factors and principles involved in the pharmacological action of poisons and drugs.

By the action of a drug or poison we understand the aggregate of the alterations which it causes in the functions of the whole body. The action of curare is directed with unusual precision against a single kind of organ, the motor nerve-endings. This we call an ELECTIVE action. When injected subcutaneously, curare does not act on the subcutaneous tissues at the point of injection, nor, when given intravenously, does it act on the blood-vessels. It has thus no local action, but the motor nerve-endings in the whole body are acted upon wherever sufficient amounts of the drug are carried by the blood. This we call SYSTEMIC action.

Just as the ordinary dose affects only the motor nerve-endings, so too the action of a dose many times larger is limited to these same organs, all other cells in the body being unaffected or nearly so.

With many other drugs having an elective systemic action, we find a somewhat different behavior; for example, with an increase of that minimal dose of atropine which diminishes glandular secretion, the pupils dilate and the pulse-rate increases, and, after a somewhat greater increase in the dose, still other functions are affected. Here the first effect is soon followed by effects due to actions on other organs, while with curare the systemic action (except with very large doses) is exerted on a single kind of organ, as it is in a very high degree elective. Curare also illustrates well how the results of the

same pharmacological action may differ in different species of animals, the frog surviving for days in spite of complete paralysis of all voluntary muscles, whereas, in warm-blooded animals, asphyxia results from this identical action. Here we have illustrations of PRIMARY or DIRECT, and SECONDARY or REMOTE or INDIRECT pharmacological actions or illustrations of pharmacological actions and their effects.

THE NATURE OF PHARMACOLOGICAL ACTIONS

The analysis of the curare action as given above consists in a determination of its seat of action in a physiological sense, such determination of the seat of action being always the first problem in pharmacological research. The nature of the action in the case of curare paralysis, as also in the case of all other pharmacological actions, is to be considered as a chemical or physico-chemical interaction between the drug and the constituents of the cell. In the case of curare, as in most cases, it is not yet known which elements of the functioning cell are involved in the reactions. However, this lack of precise knowledge in no way affects the conception that assumes a chemical or physical change in the affected organs whenever a pharmacological action takes place. In some instances it is known with what cell elements the drug reacts; for example, in the case of the action of carbon monoxide on the blood-cells, it is the hæmoglobin which enters into the chemical reaction. In other cases the chemical properties of the drug enable us to deduce with considerable precision the chemical substances in the cell which are especially involved in the chemical reaction occurring. In this way the cytotoxic action of oxalic acid has led to a recognition of the importance of the calcium salts for cell life. In the case of the alkaloids, on the other hand, we know only the place where the reaction takes place but not the reacting constituents of the protoplasm.

Even in the analysis of the action of curare, it must be admitted that the determination of the seat of action is not absolutely definite, for the nervous end-organs are complex structures containing nerve-fibrils which pass into the true end-organs, the nerve-plates, these last finally send branching filaments into the muscle-cells (*Herzen, Joteyko, Langley*).

In all cases an alteration of the protoplasm must be assumed, and we must conceive that this protoplasm attracts to itself the drug present in a definite, although very moderate, concentration in the blood. Curare gives us a good example of this dependence of the reaction between the protoplasmic constituents and the drug on a definite adequate concentration of the drug in the blood and the tissue fluids, the so-called "threshold value." If, after subcutaneous or intravenous injection, the concentration of the drug in the blood reaches this adequate concentration rapidly enough, the chemical or

physical reaction occurs and the pharmacological reaction results. If, however, the same dose distributes itself throughout a larger animal, or if it enters the blood gradually and at the same time is removed from it by the activity of excretory organs, as for example when curare is absorbed from the stomach and excreted by the kidney, then this adequate concentration in the blood is not attained and the pharmacological action does not occur.

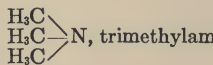
Once the curare has combined with the nerve-endings it remains combined for a considerable time notwithstanding its rapid disappearance from the blood. Here, too, in the stability of this combination, we have the expression of a chemical or physico-chemical affinity between the protoplasmic elements and the drug, but we have no exact knowledge of the nature of this affinity. At first sight the gradual disappearance of the curare paralysis appears quite as puzzling as its development. In CO poisoning the return of function is explained by the dissociation of the CO hæmoglobin, which begins as soon as the partial pressure of the CO in the blood-plasma—*i.e.*, the concentration in the neighborhood of the susceptible cell—diminishes below a certain level or is reduced to zero. In a similar manner—that is, by the conception of the combination of the drug with the cell substance as a reversible process—we must explain the gradual return of function in other cases, which have thus far not been capable of closer analysis (*Böhm*[2]).

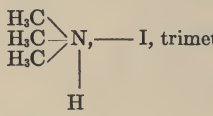
Therapeutic Use of Curare. —Many attempts have been made to use curare therapeutically, but without success. It might appear that it would be advantageous to use it to prevent convulsions due to an abnormal excitability of the central nervous system. Inasmuch as the respiratory muscles are the last to be paralyzed, it is possible, at least in experiments on animals, to maintain, even without artificial respiration, a degree of curare action which prevents ordinarily effective doses of strychnine from causing convulsions. Such treatment of strychnine poisoning, although entirely symptomatic, if combined with the removal of the poison by means of stomach lavage and with stimulation of diuresis, might be the means of saving life, for exhaustion of the vitally important nervous centres may result from the convulsions. In man, too, by prevention of convulsions by the use of curare, life might be saved in those cases of tetanus and rabies where the body is able to overcome the infection. As a matter of fact, in a number of such cases, a cessation or diminution of the force and frequency of the convulsions has followed the use of curare (*L. Vella, Busch, F. A. Hoffman, Bergell* in tetanus, *Offenberg, Penzoldt* in rabies.) If this treatment be adopted, a complete paralysis of all the motor nerve-endings must be avoided, for, if the respiratory muscles be paralyzed, long-continued artificial respiration will be necessary and this alone can jeopardize life. Unfortunately, owing to the

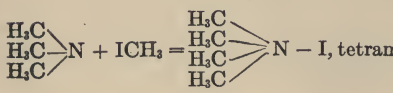
differences in the activity of different specimens of curare and their tendency to deteriorate, even physiologically assayed preparations cannot be used with any certainty as to dosage.

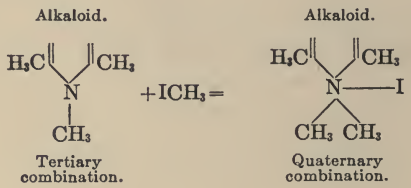
Many other substances resemble curare in their action, and in their study certain interesting relationships between chemical constitution and physiological action have come to light.

The characteristic action of almost all ammonium bases is the paralysis of motor nerve-endings. This is not possessed by chloride of trimethyl-ammonium, a tertiary base (*Santesson u. Koraen*), but the salts of tetramethyl-ammonium and those of the tetraethyl-ammonium (*Rabuteau, Jodlbauer, Jordan*), in accordance with the quadrivalency of these bases, possess this action. Moreover, in the case of many alkaloids, such as strychnine, morphine, quinine, etc., their transformation into tetrabasic substances, such as methylstrychnine, methylmorphine, etc., endows them with a more or less marked curare action (*Brown and Fraser*). In this connection, it is of interest that curarin is tetrabasic, while curine, which does not possess this characteristic action, is tribasic, but acquires it when methylated.









It would appear, therefore, that the power of paralyzing motor nerve-endings is a property possessed especially by quaternary bases. This is apparently not due to their containing certain elements or groups, but rather to the increased basicity resulting from the change from a tertiary to a quaternary base (*Führer*), for the analogous bases, which in place of nitrogen contain arsenic (*Bürgi*), antimony, phosphorus (*Vulpian, Lindemann*), iodine (*Gottlieb*), or sulphur (*Curci*), (arsonium, stibonium, phosphonium, ionium, and sulfine bases), act like curare. It would be a mistake, however, to conclude that only this especial type of base possesses curare action, for the same action is exerted by a group of bases which are not quadrivalent (chinoline, pyridine, piperidine, and others) (*Moore* and *Prow*), while non-basic substances,—*e.g.*, camphor in the frog,—and lastly certain poisons of animal origin, such as the venom of the cobra and of the spectacled snake, also produce curare-like actions (*Vollmer, Arthus*). It is, however, probable that these substances, which are chemically so different, do not all act on the same elements or substances in the nerve-endings but on chemically different substances or elements in them.

STIMULATION OF MOTOR NERVE-ENDINGS

The motor nerve-endings in striped muscles are also susceptible of excitation by chemical substances. This has long been known of guanidin (*Gergens u. Baumann*), while the fibrillary muscular twitchings caused by physostigmine are also due to excitation of the motor nerve-endings (*Rothberger*). Of especial interest is the reciprocal antagonism of curare and physostigmine (*Rothberger, Pal*). Animals poisoned by curare to the degree of complete cessation of respiratory movements, in which indirect muscle excitability (by centripetal stimulation of the sciatic) has disappeared, after the intravenous administration of physostigmine, show spontaneous respiratory movements and normal muscle excitability, while the administration of a fresh dose of curare again brings about complete paralysis.

One could think of this play of antagonism between these two drugs as resulting as follows:

As physostigmine possesses a similar affinity for the nerve-endings, it displaces curare from its combination with these structures. According to the doses administered,—that is, in accordance with the effective amounts present in the cells,—the opposite action may occur, curare replacing the physostigmine. It is, however, also possible that the two drugs act in different places or on different substances in the terminal nervous organs, and that curare places, as it were, a resistance coil in the end-plates while physostigmine increases the excitability of still more peripherally situated portions of the terminal organs. If the latter hypothesis represents the facts, a motor impulse, although able to pass through a portion of the end-organ which had been rendered more resistant by curare, would reach the terminal portion of the nerve in the muscle-cell only in such diminished force as not to cause an effective excitation. If, however, these terminal portions had been rendered more excitable by physostigmine, even the weakened impulse would produce an effect, while a further increase of the interposed resistance, resulting from further dosage with curare, would prevent entirely the passage of motor impulses to this terminal portion or weaken them to such a degree that they would no longer be effective. Certain other bases, among them choline, overcome the curare paralysis by an action similar to that of physostigmine (*Rothberger, Pal*).

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CHAPTER II

PHARMACOLOGY OF THE CENTRAL NERVOUS SYSTEM

In the study of the pharmacology of the motor nerve-endings, it has been shown that in these nerves the capacity of transmitting centrifugal impulses to the muscle-cells may be depressed or diminished by curare or increased by other substances. In all other nervous organs also and especially in the nervous centres, drugs and poisons may cause STIMULATION or DEPRESSION, but never a qualitative change of function. However, although pharmacological actions in the central nervous system may consist only in depression or stimulation of nervous elements, it would be a mistake to conclude that there can, therefore, be but two types of pharmacologically active substances, of which one increases while the other depresses the activity of the whole central nervous system, as exemplified by the old classification of sedatives and excitants.

Different drugs, even though acting on the central nervous system in but one sense, differ much from each other on account of differences in the order in which their actions on different functions develop, this order being characteristic for each drug or group of drugs. Owing to the different susceptibility of different parts of the central nervous system to each individual drug, there results a great variety in the effects which may be produced.

Often certain parts are so much more susceptible to the action of a drug than all other parts of the central nervous system, that from a therapeutic point of view only the action of this portion need be considered. For example, apomorphine in certain dosage acts directly only on the vomiting centre, leaving all other parts of the central nervous system practically unaffected, while small doses of morphine act almost exclusively on the function of pain perception (probably located in the cerebral cortex) and on the respiratory centre, its numerous other actions on the other centres resulting only from larger doses. Quite as sharply limited are the primary effects of numerous other drugs, and, as a result of the differences in the sensibility of the different elements which are affected, the whole picture of the pharmacological action of each drug is distinguished by the characteristic order in which changes occur in the different functions.

The wonderful number of varieties of drug actions is also due to the fact that different parts of the central nervous system may not only differ quantitatively in their susceptibiliy to a given drug, but also to the fact that often enough certain centres may be excited and others depressed by identical doses of a given drug. Such a combination of depression of certain functions and stimulation of others

is very commonly caused by toxic doses of those drugs which act especially on the central nervous system. Conditions varying from those resembling tipsiness with moderate excitement to those with most violent delirium or convulsions or with complete loss of consciousness are examples of such pharmacological actions, and are observed, for example, in atropine or in camphor poisoning.

Numerous poisons have the peculiar property of causing, in the later stages of their action, or in larger dosage, a depression of those very centres which they primarily stimulate. The action of prussic acid on the respiratory centre is a typical example of such behavior. Such observations have occasioned much discussion as to whether or not this is a general law,—that is, whether every chemical irritation must in the beginning cause a stimulation. Inasmuch as no increase in the excitability of the nerve-endings can be observed at the commencement of the curare action nor in that of the respiratory centre at the beginning of the morphine action, it is not possible to conclude that this is a universal rule. The qualitative differences in the reactions and the quantitative differences in the susceptibility of the different but functionally related tracts of the central nervous system may be explained by the justifiable assumption that their protoplasm possesses different chemical and physical affinities for different drugs. However, our knowledge of the chemical physiology of the central nervous system is too incomplete to permit even rough guesses as to the nature of these affinities. From these differences in their chemical behavior toward the different drugs, it may be concluded that probably each nervous protoplasmic element which possesses a special function has certain peculiarities in its composition. The elective absorption of dyes—*e.g.*, the vital staining with methylene blue—is a visible demonstration of such differences in the affinities of different elements of the central nervous system.

From the above, it is evident that the ANALYSIS OF PHARMACOLOGICAL ACTIONS IN THE CENTRAL NERVOUS SYSTEM will consist mainly of a determination of the points or functions acted upon, and of the order in which the different ones are affected. It seems well to start with a consideration of a stimulating pharmacological action, that of strychnine.

STRYCHNINE

Strychnine and a second much less active alkaloid, brucine, occur chiefly in various strychnos varieties (order Loganiaceæ) and especially in the seeds, wood, and bark of Strychnos Nux-vomica, indigenous in Southern Asia. Nux vomica, the dried seed of this tree, contains about 1.3 per cent. of strychnine and 1.7 per cent. of brucine.

The bark contains even larger quantities of brucine, while the seeds of Strychnos ignatii, S. tieute, and other strychnos varieties contain as much as 2 per cent. of strychnine and also brucine. Some Malay tribes have used these in the preparation of arrow-poisons.

Strychnine itself is an alkaloid, crystalline, efflorescent, and odorless, but with a very bitter taste. It is poorly soluble in water and may be extracted from it by chloroform. Its salts are readily soluble in water, the sulphate being the one most used. When dissolved in concentrated H_2SO_4, strychnine gives, on addition of a trace of potassium bichromate, a violet color, which changes gradually to blue and then to green.

The DOMINANT ACTION OF STRYCHNINE is essentially an elective one on the reflex arcs in the central nervous system. If the reflexes are depressed as a result of pathological conditions, small doses of strychnine may restore them to their normal condition, while toxic doses cause such an exaggerated irritability of the reflex mechanism that a reflex causes not only the ordinarily resulting normally coördinated movements occurring with abnormal intensity, but also other similarly exaggerated movements not normally resulting from such reflex. Normally, excitation of reflexes in the cord causes responses of various sorts, occurring according to fixed laws, so that, after stimulation of a given sensory nerve, certain movements and combinations of movements occur. When the action of strychnine has fully developed, however, each single stimulus affecting the sensory organs causes a simultaneous contraction of all the skeletal muscles.

ACTION IN THE FROG.—If 1/10 to 2/10 mg. of strychnine be injected into a frog, he soon shows an abnormal reaction whenever he is touched. While a normal frog, if lightly touched, does not move at all, and responds to stronger tactile stimuli only when they affect especially sensitive parts, after strychnine the very lightest touch is enough to cause violent reflexes. Slight shaking, which ordinarily is without effect, causes a pronounced muscular response, for the excitability of the reflex mechanism has been increased. Finally, any sensory stimulus produces a tetanic convulsion.

By TETANUS is meant a tonic contraction of all the skeletal muscles, lasting seconds or minutes, which is caused by a rapid succession of single muscular contractions. The individual convulsions may be separated from each other by longer or shorter periods, which, however, may be so short that for a considerable period the body remains absolutely stiff and motionless. Inasmuch as, when all the muscles contract simultaneously, the extensors overcome the flexors, the extremities and the trunk both assume the position of extension.

A frog may lie for many days in this condition, as the respiration through the skin suffices for its sluggish metabolism, and as the tetanus itself, even when long continued, does not kill the frog. When produced by other poisons, such as tetanus toxine or certain polysulphides (*Harnack*), the tetanus may last for weeks and the frog continue to live. Small doses of strychnine also may cause a condition of maximally increased reflex excitability which lasts for from 8 to 14 days, during which every stimulus excites a tonic convulsion

(*Bongers*). As somewhat larger doses of strychnine rapidly cause death in frogs, it is, therefore, clear that the fatal result is due not to the tetanus itself, but to other actions of strychnine which will be discussed later.

A closer ANALYSIS OF THE ACTION shows that its seat is in the cord. Its central nature is demonstrated by the fact that a leg isolated from the circulation before the injection of the drug is, like the others, involved in the convulsions, while as soon as its nerves are severed this is no longer the case (*J. Müller, Kölliker*). The convulsions in a decerebrated frog differ in no way from those in an intact one, but, on the other hand, if the spinal cord be destroyed, the tetanus ceases. It follows that the chief seat of the action of strychnine lies in the cord, but this does not exclude the possibility that strychnine increases reflex excitability in the higher parts of the central nervous system as well as in the cord.

That the tetanus is a convulsion of reflex origin and is not caused by direct stimulation was demonstrated in 1846 by *Hermann Meyer,* who observed that after division of all the posterior nerve-roots in frogs, convulsions did not occur, while the slightest touch to one of the central stumps of the roots caused most violent convulsions. The convulsions cease and the frogs remain relaxed if the skin be anæsthetized by painting with a solution of cocaine, all sensory stimulation via the nerves of touch being thus prevented (*Poulsson*). Moreover, after very small doses, 1/50 to 1/100 mg., the simple avoidance of all stimulation or other irritation is sufficient to prevent the outbreak of convulsions. It is thus clear that the central reflex mechanism has been rendered immensely more sensitive to the normal physiological stimuli and that a direct stimulation of the motor ganglia in the anterior horns is not produced by the drug.

This might be concluded simply from the character of the muscular contractions in strychnine convulsions, for these are not irregular or fibrillary twitchings, but are coördinated simultaneous contractions of entire groups of muscles. From what is known of the structure of the spinal cord, such contractions can result only with the aid of receptive neurons which are everywhere connected with one another by countless anastomoses and collaterals and which, when normally or abnormally stimulated, send their messages to motor neurons lying more or less distant from them, according as the paths are open for their passage or are more or less obstructed. On the other hand, motor neurons are incapable of independently transmitting exciting stimuli to each other (*Exner*[1]), for no one has ever, by stimulating a motor nerve, succeeded in causing stimulation in another motor neuron. These conditions and relationships are schematically illustrated in Fig. 2. *Houghton* and *Muirhead* have also brought experimental proofs, based on these anatomical facts, that strychnine can act only on the branching receptive portions of the reflex arc.

If a trace of strychnine is placed on a limited portion of the exposed cord of a frog in which the blood and lymph circulation have been abolished, after a few seconds the following phenomena are observed. If a portion of the skin corresponding in its nervous supply to the poisoned segment of the cord be touched, a convulsion involving the whole animal occurs. If, however, any other part be touched, only the usual reflex movements result, and even the muscles controlled by the poisoned segment react in an entirely normal manner. Inasmuch as the discharge of nervous energy causing contractions of all the muscles spreads only from the poisoned segment of the cord, that is to say, produces in all the unpoisoned motor cells of the anterior horn a stimulus resulting in tetanic contraction of the muscles, and as this can result only through the agency of the receptive cell mechanisms and their manifold anastomoses, it necessarily follows that these receptive cells are the seat of the abnormally violent and unrestrained discharge of nervous energy.

At a later day, *Baglioni*[1], in certain most instructive experiments, obtained entirely similar results, using an isolated nerve and spinal cord preparation connected only with the hind legs. Under these conditions he found that strychnine acted only when placed on the dorsal side of the cord and not when placed on the ventral surface. An apparent contradiction of these views is furnished by an experiment of *Sherrington*. The cord of a dog was isolated from all external impulses by cutting it across and dividing all the posterior spinal nerve-roots. After such preparation, strychnine caused typical tetanus, even six weeks later when all the afferent neurons had completely degenerated (*H. Meyer*, unpublished experiments).

The contradiction is, however, only an apparent one, for of the mechanisms which transmit stimuli, only those neurons coming from the periphery and those coming from the brain degenerate, while the independent "relay cells" (*Schaltzellen, Exner's*[2] a-cells) with their continuations remain unaffected. These cells accordingly must be able to receive chemical stimuli from the blood or mechanical ones resulting from vibration and to coördinate and transmit them to the cells in the anterior horns. These "shunting" neurons (Schaltneurone) may be assumed to be the seat of the strychnine action.

Fig. 2.—Diagrammatic representation of spinal cord. Blue: Receptive cells and tracts. Red: Motor cells.

From consideration of these various phenomena, it may then be concluded that strychnine affects the receptive neurons of the cord in a special fashion and with a double effect: firstly, in place of normal, temporary, and sub-maximal contractions, only maximal and persisting contractions result from reflexes; and, secondly, these reflex tonic muscular contractions are not confined to that muscle group which is normally controlled by the stimulated sensory neuron, but they involve all the muscles of the body and, as should be especially noted, even the antagonistic muscles.

Theory of the Action of Strychnine.—For the better understanding of these phenomena, one may assume that certain inhibitions in the receptive organs of the cord are removed by strychnine. It is very probable that in the sensory receptive cells there are certain inhibitory mechanisms, which ordinarily prevent the immediate discharge of all their stored-up energy whenever they are stimulated.

For this reason, they function only intermittently, or, as *Baglioni*[2] expresses it, these sensory cells have a refractory period, in contradistinction to the motor ganglion cells in the anterior horns, which when stimulated can discharge energy continually (*Birge, Baglioni*[3]). This is the reason why, under normal conditions, a tonic contraction of a muscle can never be caused reflexly,—that is, through the sensory tracts,—but is readily induced by direct stimulation of the motor ganglia. If this sensory mechanism be so affected by strychnine that it loses this property of becoming refractory, it may then discharge stimuli continually and excite tonic contractions.

Still other inhibitions of different kinds are removed by strychnine,—for example, those which normally prevent the stimulation of one sensory neuron from spreading at will to other parts by way of secondary paths. These secondary paths extend in so many directions and are so branching that any particular sensory impulse from any sensitive point could probably be carried to all the motor cells in the central nervous system. As a rule, however, such impulse passes only along the shortest or most open path which runs to the physiologically more nearly related motor cells and passes to all others by way of these secondary paths only in imperceptible and ineffective intensity (*Exner*[3]).

Moreover, as a result of Sherrington's fundamentally important investigations, it has been shown that normally the excitation of an agonist (*e.g.,* flexor muscle) is regularly accompanied by inhibition of its antagonist (*e.g.,* the corresponding extensor), and that, therefore, normally, both cannot reflexly be caused to contract. One may look upon this as due to the fact that between two antagonistically coördinated motor cells there is always a reciprocal inhibitory mechanism which so acts, that when a cell (*m,* Fig. 3) is excited, the antagonistic cell (m_1) is automatically inhibited.

This mechanism is indicated diagrammatically in the figure by the two arrows with the minus sign. Normally, the impulse from the spinal ganglion reaches in effective strength only the cell *m,* while to m_1 there comes only an inefficient impulse, for the path is not opened, or is obstructed by certain obstacles, such as interposed cells, which are indicated in the diagram. Therefore, cell *m* is stimulated, while in some way or other m_1 is inhibited. As a result of the action of strychnine, however, the side path to m_1 (as also all other side paths) is freed of all obstacles or inhibitory influences, and permits the passage of just as much stimulating impulse as does the main path running to *m.* Thus, both cells *m* and m_1 receive equally strong stimuli, and their reciprocal intracentral inhibitory mechanisms compensate each other, as it were. As a result agonist and antagonist both contract.

Action in Higher Animals.—The action of strychnine on reflex excitability is practically identical in all vertebrates, but in the

higher animals there is more evidence of increased sensitiveness of the reflexes in the brain, especially of the reflexes resulting from stimulation arising in the more highly developed organs of sense.

In the higher vertebrates the susceptibility to strychnine is much greater than in the frog. The lethal dose for the latter is 2 mg. per kilo., while for rabbits, dogs, and cats it is from 0.6–0.75 mg. per kilo. On the other hand, birds are in the highest degree insusceptible to strychnine administered by mouth (*Falck*).

After receiving an injection of an effective dose of strychnine, a rabbit soon manifests a peculiar uneasiness. He cocks his ears, raises his head, etc. Soon, quite suddenly and following any sort of stimula-

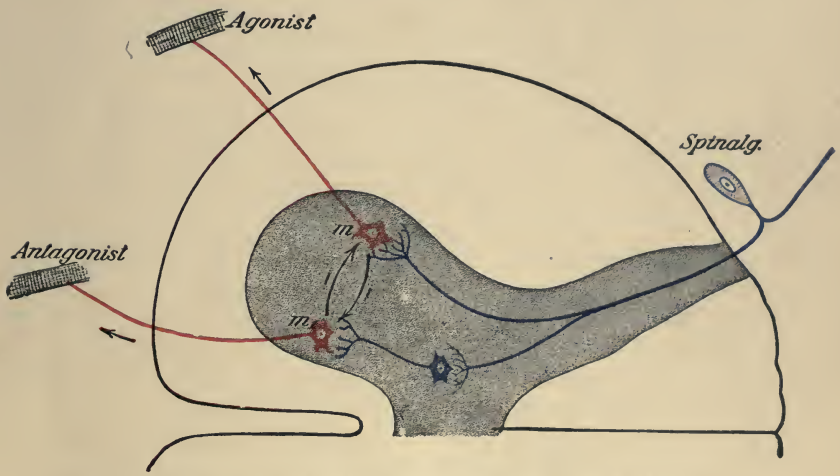

Fig. 3.—Diagram of the intracentral inhibitory mechanism of the spinal cord.

tion, a tonic convulsion occurs, the extremities becoming stiff in a position of extension, and the body rigid in a state of opisthotonos. The convulsions may last a minute or longer, and during them the tremor of the muscles may be felt.

As all the respiratory muscles take part in the tonic contractions, respiration is prevented and the symptoms of asphyxia appear, if the convulsion lasts long enough, but, as a rule, the animals do not die during the convulsion. More often, after more or less numerous convulsions a condition of paralysis develops. The reflex excitability steadily diminishes, the blood-pressure falls and remains very low, and the respirations become constantly weaker until they stop entirely.

In addition to these characteristic actions on the reflex mechanism of the cord, in the higher animals strychnine exerts a similar exciting action on the REFLEX CENTRES in the CEREBRUM and MEDULLA. The

blood-pressure rises during the convulsions and the pulse becomes slow, even when asphyxia is prevented by artificial respiration. Also when the convulsions are prevented by curare, there are periodic recurrences of the rise in blood-pressure and of slowing of the pulse (*S. Mayer*) for which the increased excitability of the vasomotor and vagus centres is responsible. A similar action on the RESPIRATORY CENTRE also occurs, for it may be shown experimentally that after the excitability of the respiratory centre has been markedly depressed by such a drug as morphine, strychnine in doses which are not large enough to cause convulsions will bring about a marked increase in the excitability of this centre (*Biberfeld*).

The action of strychnine on the different SPECIAL SENSES is of considerable therapeutic importance. Touch, smell, and taste all become more acute, and the sensitiveness of the visual organs is improved so that the field of vision is enlarged and the ability to distinguish colors is increased. *Filehne* has shown that these effects, except those on vision, are the results of an action on the central sensory tracts in the cerebrum. In the eye the drug acts directly on the retina, which, as is well known, may be looked upon as a portion of the cerebrum. Inasmuch as this increase in the sharpness of the senses results from an action of strychnine on the sensory centres in the brain, the increased sensibility of the senses appears entirely analogous with the increased excitability of the sensory organs in the cord.

PARALYTIC ACTION OF STRYCHNINE.—Strychnine, however, exerts still other actions on the nervous system. Mammals, as well as frogs, die in a state of paralysis which follows the convulsions. This has often been explained as due to an exhaustion of the nervous system as a result of the convulsions. While it is a fact that an increased tendency to exhaustion goes hand in hand with the increased excitability of the reflex organs, for the unchecked discharge of impulses readily leads to an exhaustion of the energy in the receptive organs which have no time to rest or to form anew those substances consumed by their discharge of energy, still the exhaustion of the cord resulting from the convulsions in one way explains the rapid paralysis occurring in frogs after large doses of strychnine. Neither does it explain the fact that in mammals death results from respiratory and vasomotor paralysis, which may occur after only a few convulsions. These phenomena result rather from another later action of strychnine, a paralyzing one, which is more in evidence, as compared with the convulsant action, the larger the amounts of the poison absorbed. →

In such case a general paralysis develops after tetanus of short duration. In frogs in which this paralysis is not fatal, a tetanus

lasting for days may be observed after the paralysis has passed off. This paralysis also has nothing to do with that depression of the heart which occurs after large toxic doses of strychnine (*Igersheimer*). *It is the final cause of death in cases when very large amounts of the poison have been taken* (*Poulsson*).

After large doses of strychnine a "curare" action occurs in the frog, which is much better developed in the Rana esculenta than in the R. temporaria.

It is a noteworthy fact that at a time when the reflex excitability from tactile skin irritation is highly exaggerated, chemical irritation of the skin (by acetic acid) and other painful stimuli (by cutting) produce no effect. Moreover, irritation of the viscera, which in normal frogs causes defective movements, has no effect in strychninized ones. It is, therefore, apparent that the different receptive systems in the spinal cord are variously affected by this drug. The perception of a painful stimuli is from the start diminished as a result of a central depressing action. Only for the stimuli through the ordinary senses does the nervous system become over-excitable (*T. Sano*).

Toxicology.—Strychnine poisoning in man occurs usually as a result of taking the poison by mistake or as the result of exceeding the permissible medicinal dose. The premonitory symptoms are feelings of drawing and stiffness in certain muscles, hypersusceptibility to sensory impressions, restlessness, and trembling. After larger doses (more than 0.03 gm.) exaggerated reflex excitability and a marked feeling of anxiety develop and suddenly the attacks of general tetanic convulsions start. The convulsions may last from several seconds to two minutes, and, as during them respiration ceases, death may result from asphyxia. In the intervals between the convulsions the consciousness is maintained, but during the convulsions the increasing asphyxia beclouds it. Usually after three or four severe convulsions death results from exhaustion of the nervous system (*Denys*). The mean lethal dose for an adult is from 0.1–0.12 gm.

In the treatment of strychnine poisoning the first aim is to prevent the occurrence or to lessen the violence of the convulsions, which in themselves jeopardize life. This may be accomplished either by quieting the hyperexcitable centres by the administration of narcotics or by interfering with the passage of the abnormally violent motor stimuli, which may be done by depressing the motor nerve-endings with curare. Theoretically the treatment with curare should be the more efficient treatment for strychnine poisoning, for, as strychnine itself exerts a paralyzing action on the nervous centres, the administration of narcotic drugs increases the danger of the development of such central paralysis. However, as stated in the discussion

of curare, it is difficult to determine the dosage of this drug exactly enough to secure cessation of the convulsions without also stopping the respiration.

If the convulsions have not already started, chloral should be given by mouth or by rectum, or, if nothing else is at hand, alcohol in one form or another. All noises, draughts, or sensory stimuli are to be avoided, and finally, by apomorphine or by lavage, any unabsorbed poison should be removed from the stomach. [Even although the convulsions have not yet started, the administration of apomorphine and the resulting vomiting, or the use of the stomach-tube, is extremely liable to start up the convulsions in an unanæsthetized patient.—Tr.] If the convulsions have already started, chloroform anæsthesia should at once be induced and the stomach emptied by lavage. As the chloroform anæsthesia passes off, chloral hydrate should be given by rectum and measures taken to stimulate diuresis, in order that the strychnine may be excreted while the patient is sleeping under the influence of chloral.

In animal experiments artificial respiration may bring about a cessation of the convulsions caused by strychnine. The breathing of pure oxygen also moderates or prevents the occurrence of the convulsions, while an insufficient oxygen supply augments their violence (*Osterwald*).

Therapeutic Uses.—Among the therapeutic indications for strychnine is its employment in amblyopias and amauroses without anatomical change or in incipient optic atrophy, in which conditions its curative or helpful action has been certainly demonstrated. Moreover, in cases of impaired hearing of central origin, improvement has been claimed from its use in dosage up to 0.01 gm. per dose (!) and 0.02 gm. per diem (!) of strychnine nitrate, subcutaneously injected. Its use in motor paralysis is recommended from many sides. *Naunyn,* among others, reports good results in pareses, but never in complete paralysis, from the daily injection of 0.01 gm. in series of 10–12 injections, with 6–8 days' intervals intervening. It would thus appear that this drug favorably influences the re-establishment of motor functions only when the interruption of the motor tract is not a complete one. Strychnine is also used in cases of paralysis or weakness of the sphincters and in nocturnal enuresis.

In atony of the alimentary canal the effect of strychnine is uncertain. For this indication it may be used in the form of the extract 1–5 cg. (!) per dose up to 0.1 gm. (!) per diem. The employment of the tincture in various affections of the stomach and intestines rests probably upon its action as a bitter.

The employment of STRYCHNINE as an ANTIDOTE in NARCOTIC POISONINGS, especially in poisoning with chloral hydrate, alcohol, centrally depressing snake-poisons, etc., rests on a better physiological foundation than the above-mentioned therapeutic uses. In other countries strychnine is used much oftener for such indications than in Germany, where the preference is given to the harmless caffeine. As the excretion of strychnine by the kidney takes place extremely slowly (*Ipsen*), it can accumulate in the body when administered for a considerable period.

[That strychnine is of value as a stimulant in various conditions of depression of the central nervous system, especially in infectious disease, is firmly believed by many physicians, of whom the translator is one. That its value is often over-estimated is probably true, but the weight of clinical evidence certainly is in favor of its usefulness in such indications. Nothing, however, can be expected from small doses, such as 1.0 mg. 3 to 6 times a day, which are the usual doses given. Doses three or more times as large are, as a rule, the only ones capable of producing real benefit. Naturally, when such larger doses are given, the patient should be carefully watched, and at the first sign of exaggerated reflex excitability the drug should be diminished or stopped. In this connection the translator would call attention to the antagonistic effects of alcohol and strychnine, which would appear to him to indicate that it is irrational, at least in respect to the effects on the central nervous system, to give to a patient large doses of both of these drugs.—TR.]

BRUCINE, which occurs together with strychnine in nux vomica, is chemically closely related to it, being probably dimethyloxystrychnine (*J. Tafel*), and its physiological action is similar to that of strychnine, but much weaker.

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GENERAL CHARACTERISTICS OF ALKALOIDS

As has been mentioned, strychnine is a typical alkaloid, and, as many of our most important drugs belong in this group, a brief description of their general characteristics will be advantageous at this time.

The alkaloids are nitrogenous bases, chiefly of vegetable origin. Commonly, however, this term is applied only to those vegetable bases which exert powerful physiological actions, although it is also applied to certain bases formed by the decomposition of animal tissues, the so-called ptomaines, or cadaveric alkaloids.

Most alkaloids contain C, N, H, and O, but a few contain no O. In general they may be considered to be substituted ammonias or ammonium bases, the nitrogen in most of them entering into the formation of such closed carbon rings as those of pyrrhol, pyridine, quinolin, etc.

As a result of their basic character they, like ammonia, readily form salts with acids. These are broken up by ammonia, fixed alkalies, and other bases, in accordance with their mass action and their basicity. In this way the insoluble alkaloids may be precipitated from aqueous solutions of their salts.

In contradistinction to the free alkaloids, these salts are, as a rule, soluble in water and in alcohol, but are insoluble in benzene, ether, chloroform, and amyl alcohol, in which the free alkaloids are more or less soluble. The usual methods of isolating alkaloids are based on these solubilities and insolubilities.

After isolation the alkaloids are identified by various methods, among which only the color-reactions and physiological tests need be mentioned here. As the color-reactions often are ambiguous unless the alkaloid is absolutely uncontaminated by other substances, the physiological tests are often more positive and more definite than the tests based on color-reactions. This is notably the case with strychnine (*Ranke*).

Tannic, phosphomolybdic, phosphotungstic, and picric acids form with most alkaloids, even when highly diluted, salts which are very insoluble in water and which consequently are precipitated. The chlorides of platinum and gold and the chlorides and iodides of mercury, bismuth, and zinc form with the chlorides of most alkaloids very insoluble double salts. These reagents may therefore be used to determine the presence of alkaloids.

CONVULSANTS

Besides the toxic excitation caused by strychnine, the typical convulsant, there are other types of toxic excitation of the central nervous system which may excite convulsions, which, however, are not precipitated by sensory stimuli, and hence are not of a reflex character. Such convulsions differ from those produced by strychnine in not being characterized by a simultaneous contraction of all the muscles in the body (including the antagonists), for in them only certain groups of muscles contract. As previously stated, in strychnine convulsions all the muscles, both agonists and antagonists, contract simultaneously, a tetanic or tonic convulsion resulting. This simultaneous contraction of all the muscles finds its explanation, as already stated, in the unhindered spreading of the sensory stimulus over all the afferent paths and bypaths, this resulting in an equally simultaneous excitation of all the motor centres, even the antagonistic ones. On the other hand, certain other convulsant poisons, without interfering with the inhibition of the antagonists, cause involuntary muscular movements similar to those of orderly normal motions. Such convulsions are known as clonic convulsions, and it is characteristic of them that their occurrence is apparently spontaneous although in reality they are caused by summation of internal stimuli. Like epileptic attacks, after a short period they cease for a time, and therefore are described as being of a periodic or epileptiform type.

In contradistinction to the tonic convulsions which are of spinal causation, these epileptiform convulsions are excited by conditions arising in the higher centres normally controlling voluntary movements, which in different species of animals are situated in different parts of the central nervous system.

For this reason there has arisen much confusion in the statements about the seat of action of the so-called convulsants. *Prevost* and *Batelli*, by stimulating various portions of the central nervous system with a powerful alternating current, endeavored to determine the parts of the central nervous system from which clonic, and those from which tonic convulsions could be excited. In full-grown dogs and cats, these authors found that clonic convulsions resulted only when the cortical motor regions were stimulated, while stimulation of the centres lower down caused tonic convulsions. On the other hand, stimulation of the cerebral cortex in rabbits, guinea-pigs, and new-born dogs and cats was not followed by clonic convulsions, but these did occur when the medulla of these animals was stimulated. Stimulation of the spinal cord may cause clonic convulsions in frogs, but only tonic contractions in the higher animals (*Samaya*).

It would, therefore, appear that, in the higher animals, EPILEPTIFORM CONVULSIONS OF TOXIC ORIGIN ARE DUE CHIEFLY TO THE ACTIONS OF VARIOUS POISONS ON THE CEREBRAL CORTEX. It is, however, not impossible that such poisons may also act on the subcortical centres.

By certain experiments (*Luchsinger*) in which transverse section of the central nervous system was performed at different levels, it has been demonstrated that picrotoxin, a typical convulsant, causes convulsions not only by its action on some higher portion of the central nervous system but also by its action on centres in the cord. On the other hand, there are other convulsant

poisons whose seat of action is sharply limited; for example, the esters of morphine-glycocholic acid, which cause violent convulsions. By similar experiments these convulsions have been shown to be due to an action on certain centres in the pons, the other portions of the central nervous system not being involved (*Barnes*).

The large number of the regions, from which clonic convulsions may be excited, sufficiently explains our incomplete knowledge of the place and manner of their causation.

CAMPHOR.—Among the many substances which may cause epileptiform convulsions, camphor should be especially mentioned. In warm-blooded animals large doses of this drug cause convulsions with clonic movements of the extremities, trismus, and tonic contraction of the facial muscles, which, in their periodic character and slight danger to life, are typically epileptiform, and are rarely followed by paralysis or even marked weakness. The therapeutic action of camphor on the central nervous system depends on the fact that doses, too small to cause convulsions, stimulate certain vitally important cerebral and medullary functions. Other convulsants—*e.g.*, PICROTOXIN and coriamyrtin (from Coriaria myrtifolia)—produce similar effects (*Köppen*).

A stimulation of the CONVULSION centres may also occur AS A TOXIC SIDE-ACTION of a number of other much-used drugs. For example, in even slight ATROPINE poisoning a certain degree of motor unrest with involuntary movements of the hands and fingers occurs, while in severe poisoning there occur outbreaks of clonic convulsive movements of the extremities, trismus, and rolling and twisting movements, which may continue to recur for hours or for days. In COCAINE poisoning, too, both epileptiform and tonic convulsions may occur. SANTONIN, so widely used as a vermifuge, is also a typical convulsant and has often been responsible for poisoning in which epileptiform convulsions occur.

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CEREBRAL STIMULANTS

Wherever convulsions occur as toxic side effects, this will be mentioned in the general discussion of the drug. In this connection it should be particularly noted that the higher psychic portions of the cerebrum, the centres of conscious perception and for voluntary movement, are capable of a stimulation or of an exaltation of their excitability similar to that which the convulsive centres manifest in more advanced poisoning. The earlier stages of such actions may be utilized therapeutically to stimulate cerebral functions when they

are depressed. The discussion of the action of strychnine on the central perception of sensory stimulation has made it clear that certain drugs can produce such an exaltation of the excitability of such cortical centres. In an analogous fashion, stimulating drugs may bring about an improvement of the functions of those other centres on the activity of which consciousness depends. At any rate, there is at the present time no conclusive evidence which forces us to believe that the symptoms of cerebral stimulation are always only a secondary result of the depression of higher psychic centres, the inhibitory ones in particular.

The clearest evidence that a direct stimulation of the cerebral functions may occur is found in the fact that depression of the cerebrum may be combated by stimulating substances. In animals conditions of cerebral narcosis, such as are produced by alcohol, paraldehyde, or chloral, may be interrupted or overcome by the administration of stimulating drugs, even after consciousness, voluntary movements, and perception of pain are abolished and most of the reflexes, including the corneal, are markedly depressed.

In dogs, *Binz* demonstrated the antagonistic action of caffeine and alcohol, and *Mosso*, by injections of 0.01–0.02 gm. of cocaine hydrochlorate, was able to awaken dogs from the deep sleep produced by chloral. *Schmiedeberg* found that "rabbits, narcotized by paraldehyde until consciousness was completely abolished, could be so thoroughly awakened by injection of ½ to 1 mg. of picrotoxin, that they moved about in quite a lively fashion." *Köppen* succeeded in doing the same with coriamyrtin injected into rabbits narcotized by chloral, and *Gottlieb*, after injecting camphor into rabbits deeply narcotized by paraldehyde, observed the return of the reflexes (including the corneal) which had been abolished, the animals waking up and moving about voluntarily. This last-cited observation illustrates well the REVIVING ACTION OF CAMPHOR on the sensorium, which is at times observed even after its administration to patients in extremis.

THERAPEUTIC INDICATIONS.—The indications for the administration of these STIMULANTS OF THE CENTRAL NERVOUS SYSTEM are found in all acute conditions of depression which are characterized by a failure of such vital functions as those of the respiratory and vasomotor centres. Such a condition is that of the so-called collapse. The stimulating effects of CAMPHOR, CAFFEINE, ATROPINE, and other drugs, indicated in collapse, are chiefly due to their action on the circulation and respiration, and therefore this will be more fully discussed in the sections dealing with the pharmacology of those functions. However, when they are employed, they also produce a stimulation of the cerebral functions whenever it is still possible to produce any affects opposing the depression of the central nervous system.

In addition to their therapeutic actions, the drugs of this class are of importance on account of their extensive consumption in various BEVERAGES. Especially is this the case with caffeine, for even the small amounts of the drug, which are present in tea, coffee, and some other commonly used beverages, produce readily recognizable effects

on the normal central nervous system. In animals the toxic action of caffeine manifests itself by an exaggeration of the reflexes, especially the spinal ones, which is entirely analogous to that produced by strychnine. In man the toxic action manifests itself chiefly by the symptoms of its cerebral effects, restlessness and great excitement (*Curschmann*). In susceptible individuals, even small amounts produce the first stages of cerebral excitement with an increased reflex excitability. This is the reason why many individuals are unable to fall asleep as usual after drinking such beverages as tea and coffee. *Kräpelin's* delicate psychophysical analysis of the effects of tea shows that these are due almost entirely to the caffeine contained in it. Making use of methods permitting of exact measurements, he found that tea improves the perception of external stimuli and also the association of ideas. This confirms the every-day experience that caffeine favors the performance of certain cerebral functions and opposes the depressing effects of alcohol and of mental fatigue.

Caffeine is a drug whose action is almost purely stimulating. Unlike strychnine, it does not, even in large doses, cause a later stage of depression. However, a certain amount of confusion of the cerebral functions does result from poisonous doses, this indicating that such doses do exert a certain degree of depressing action of some of the brain centres. Of the other cerebral stimulants which are of practical importance, camphor is one producing similar effects with but slight late depressing action, while most of the other convulsants, when given in large doses, cause not only stimulation of certain functions of the brain but also depression of others, or else a stimulation quickly followed by depression. This is the case, for instance, with cocaine, so that in poisoning caused by it extreme mental excitement and motor restlessness are accompanied by clouding of the consciousness, while a marked depression of the central nervous system succeeds the stage of excitation. With this drug, even in the early stages of the action on the central nervous system, there is clear evidence of interference with some of the higher brain functions, so the condition may be spoken of as a cocaine "jag" (*Rausch*). Only after very small doses is its action an almost exclusively stimulating one. Such are the doses taken by the natives of South Africa when chewing coca leaves, and it is this stimulating action on the cerebrum which accounts for this custom.

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DRUGS CAUSING SIMULTANEOUS STIMULATION AND DEPRESSION OF THE CENTRAL NERVOUS SYSTEM

ATROPINE.—The symptoms produced by atropine are typical of such a combination of stimulation and depression occurring side by side in the cerebrum. A peculiar psychic confusion, with hallucinations and deception of the senses, accompanies even slight grades of poisoning by this drug, while severely poisoned individuals lose consciousness during the stage of delirium and convulsions. After the stage of excitement passes off, they pass into a half-comatose state, and in fatal cases death ensues from the paralysis which then develops. With a group of alkaloids closely related to atropine, the central action causes, after only a short stage of excitement, a depression of the cerebral functions.

SCOPOLAMINE.—This is most pronounced in the case of scopolamine (identical with hyoscine), which is widely used as a sedative and hypnotic and which in its peripheral actions closely resembles atropine. Its therapeutic usefulness results from its actions on the central nervous system, which differ from those of atropine in that with scopolamine a primary depression of certain cerebral centres is more prominent than is the case with atropine. Scopolamine may, therefore, be used to induce sleep or at least to produce a sedative effect in cases of most pronounced excitement, where other hypnotics (even opium) are ineffective.

Scopolamine is a lævorotary alkaloid with the formulæ $C_{17}H_{21}NO_4$, which occurs in the various solanaceæ. First discovered in Scopolia atropoides, but also present with hyoscyamine in Hyoscyamus niger and Duboisia myropoides, and in small amounts also in Atropa belladonna and other related plants. Chemically it resembles atropine closely. Scopolamine was formerly named hyoscine and was chiefly prepared from Hyoscyamus niger, but later investigations have established the identity of hyoscine and scopolamine (*E. Schmidt*).

Scopolamine resembles atropine closely in its peripheral effects on the pupils, secretions, etc. Its therapeutic importance is, however, due to its central actions, which are distinguished from those of atropine by a much more prominent primary depression of certain cerebral centres. For a long time it has been known that the extract made from henbane acted as a sedative,—that is, in a different fashion from the atropine and hyoscamine contained in it. Impure preparations of hyoscamine, which probably contain scopolamine, have often been used with varying success as a means of quieting insane patients. Pure hyoscine, first isolated by *Ladenburg,* was a third alkaloid obtained from hyoscyamus, and later, when proved to be identical with scopolamine, was introduced into therapeutics by *Gnauck* and others.

It has been experimentally demonstrated that scopolamine has scarcely any narcotic action in rabbits, but shortly after injection of an effective dose dogs fall more or less deeply asleep. Before going to sleep, they manifest a distinct restlessness, evidently due to hallucinations and illusions, which is accompanied by uncertain gait and staggering, briefly by a tipsy condition, which precedes the stage of fatigue and sleepiness.

Man is, however, more susceptible to the central action of scopolamine, and doses of ½–1½ mg. are usually enough to produce the required sedative effect. [Few would care to give 1½ mg. ($^1/_{40}$ gr.); at any rate, as a first dose.—Tr.] Mydriasis and paralysis of the accommodation and dryness in the mouth and throat are accompanying side effects. The drug is usually used in the form of the hydrobromide and is best administered subcutaneously.

Although one speaks of SCOPOLAMINE SLEEP, and also actually can with it induce sleep even in conditions of marked mental excitement, there is an important difference between the hypnotic action of scopolamine and that of the true hypnotics. The primary seat of action with scopolamine does not lie in the centres for the perception of sensory impressions, by an action on which the true hypnotics favor the process of falling asleep, for scopolamine primarily depresses the excitability of the motor centres. When the scopolamine action commences to develop, the patients show a relaxation of their muscles and the motor unrest ceases. Only after this do the patients sink down in a relaxed position, the breathing sometimes becoming slightly stertorous on account of the relaxation of the epiglottis and the speech a little uncertain. At this stage the patients are still conscious and are sensible of visual impressions, etc. After this sleep ensues, but is often preceded by delusions, hallucinations, and delirium.

The characteristic relaxation of the muscles observed in the earliest phases of the scopolamine action and the efficiency of the drug in combating motor excitement are in agreement with *Ramm's* statement that in dogs this drug quickly depresses the cerebral motor centres so that they no longer respond to electric stimulation.

This drug is also used with benefit in nervous diseases with symptoms of motor irritation, and especially in paralysis agitans. Its use as a substitute for atropine in ophthalmologic practice will be discussed in another chapter. A better acquaintance with the action of morphine is also necessary before the use of scopolamine in combination with morphine as a narcotic for surgical procedures and as an adjuvant for the general anæsthetics may be discussed.

THE DANGERS ASSOCIATED WITH THE USE OF SCOPOLAMINE lie in an extension of its depressing action on the respiratory centre, as also in the possibility of cardiac failure. In general, the margin between hypnotic and toxic or lethal doses of scopolamine is quite large in dogs as well as in man. Dogs, in whom 1 mg. is an efficient dose, sometimes may support 1 gramme without fatal effect. However, in

man, as also has been observed in a few cases with the dog, the individual susceptibility appears to vary greatly. In conditions of pronounced psychical excitement, not only are larger doses required, but also larger doses may be borne without harmful results.

In the PRACTICAL EMPLOYMENT OF SCOPOLAMINE, THE VARIABLE ACTIVITY OF DIFFERENT PREPARATIONS has been found quite disturbing. This is due to the great difficulty of obtaining preparations of scopolamine entirely free from contamination by the other related alkaloids, some of which have quite different and in part antagonistic pharmacological actions. Thus, Atropa belladonna contains, besides scopolamine, another alkaloid, apo-atropine (*apatropine*), which is much less powerfully mydriatic but very poisonous, causing pronounced central excitation. This alkaloid appears often to be present as a contamination in preparations of scopolamine (*Kobert*). According to *Kessel*, it is easy to detect the presence of this contamination by adding a few drops of a solution of potassium permanganate to the suspected solution, reduction indicating the presence of this particular contamination.

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MORPHINE GROUP

Among the manifold forms of cerebral narcosis produced by various agents, that produced by morphine is singular in that this drug so markedly lessens the sensibility to pain. On the other hand, morphine does not depress the excitability of the cerebral cortex in anything like the same degree as do the narcotics of the alcohol-chloroform group (see p. 43 ff.), for, long before it completely abolishes the cerebral functions, it produces such marked depression in the medulla, especially of the respiratory centre, that death ensues before reflex excitability of the cord disappears. The effects of morphine thus differ from those of alcohol and choloroform in that the different portions of the central nervous system are affected by it in a different sequence. With chloroform, alcohol, etc., first the cerebrum, then the cord, and last of all the respiratory centres are depressed, while with morphine the depression of the respiratory centres occurs simultaneously with [or previously to—TR.] the depression of the cerebrum, while the reflex excitability of the cord is depressed in a far slighter degree.

This great sensitiveness to very small doses manifested by certain of the functional tracts of the cerebral cortex is of fundamental importance for the therapeutic usefulness of morphine, for perception of pain is diminished by doses which scarcely affect the motor centres and which have no appreciable influence on the perception of ordinary sensations. Such specificity of action is not shown by the substances of the alcohol-chloroform group, for with them such analgesic effects are obtained only by doses which also cause sleep. The respiratory centre and those closely connected sensory centres which control the cough reflex show this same special sensitiveness to morphine. Consequently, morphine is primarily a pain and a cough reliever, while its hypnotic effects are produced only by larger doses.

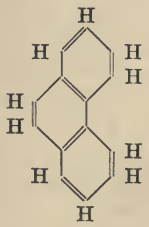
Morphine is derived from opium, the inspissated juice of the unripe fruit of the poppy, Papaver somniferum. The opium used medicinally comes chiefly from Asia Minor and the Balkan peninsula, but opium is also produced in India, China, Persia, and elsewhere. Even the common field poppy contains opium, but not in quantities sufficient to justify its commercial preparation (*Thoms*).

Opium contains a large number of alkaloids, of which about twenty have thus far been isolated. However, the main bulk of these alkaloids is made up by morphine, and the other alkaloids are either physiologically inert or else present in such small quantities that they may be disregarded. Consequently the actions of opium are essentially those of morphine slightly modified by the other alkaloids present. The usual morphine content of opium is about 10 per cent., but occasionally rises to as high as 20 per cent.

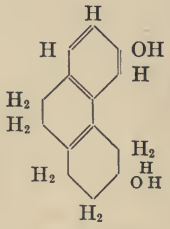
Of the other alkaloids, amounting to about 5 per cent. in all, the greater portion, about 4 per cent., is the inert narcotine. Papaverine, weakly narcotic, codeine, and thebaine, closely resembling strychnine, are present in only minute amounts. In opium these alkaloids are combined with meconic acid and are accompanied by resinous substances.

Morphine is present in all portions of the poppy plant, but as the heads ripen the morphine disappears and the seeds contain no morphine.

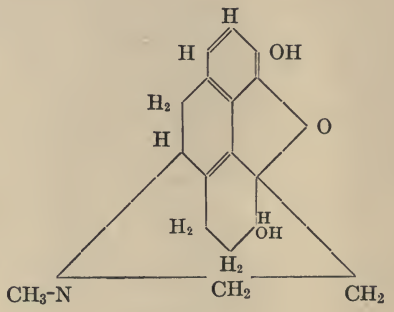
Morphine, with the empiric formula $C_{17}H_{19}NO_3$, is the first alkaloid which was prepared in pure form (*Sertürner*, 1804–16), and is a monovalent tertiary base. While its constitution has not been definitely established, the last few years have nearly solved this problem, and the morphine alkaloids are assumed to be derivatives of a hydrated phenanthrene nucleus which contains one alcohol and one phenol hydroxyl radical with the third oxygen in special bridge-like combination.



Phenanthrene.



3, 6 Dioxy 5, 6, 7, 8, 9, 10 Hexahydrophenanthrene.



Morphine (?).

In codeine the alcoholic hydroxyl is methylated, and in thebaine both hydroxyls are methylated.

Free morphine is but slightly soluble in water, more so in alcohol, acetic ether, chloroform, and amyl alcohol. Its salts are readily soluble in water and readily crystallizable, the hydrochlorate and sulphate being the ones most used. The addition of ammonia or of the caustic alkalies to solutions of its salts precipitates the free base, which is redissolved by an excess of NaOH or KOH. It is readily oxidized by oxidizing agents.

In vertebrates the susceptibility to morphine increases with the higher development of the central nervous system. In order to produce distinct effects in a frog of 30 gm. weight, doses must be administered which would seriously poison adult human beings. Observations on the frog show that the action of this drug is most pronounced in those functional tracts which are most highly developed and which ontogentically are last to develop.

Effects on the Frog.—If 0.03–0.05 gm. of morphine hydrochlorate be injected into a frog, the first effect noted is the cessation of spontaneous movements. The frog no longer seeks to escape, although when stimulated he can carry out well-coördinated and powerful movements, at this stage behaving as if decerebrated. Next disturbances in the coördination of complex movements develop. The frog no longer sits in the normal position, and jumps clumsily, behaving as if the corpora quadrigemina had been removed. As the toxic action develops still further, the frog is no longer able to leap, although still able to turn over when placed on its back, but only slowly and helplessly, as after removal of the cerebellum. Finally, when laid on the back, it can no longer turn over, respiration ceases, and the cranial nerve reflexes (*e.g.*, corneal reflex) disappear, although the spinal reflexes persist. At this stage the condition is similar to that of a frog after the medulla has been removed. Finally, the spinal reflexes also disappear. In the first stage of the action of morphine, the depression affects different parts of the central nervous system successively, commencing with the cerebrum, much as occurs when different portions of the central nervous system are removed in regular order (*Witkowski*). Naturally, the elimination of the different functional tracts does not take place so precisely under the influence of the drug as after operative removal, for the narcotic action in one part of the brain commences before it has been completely developed in another portion. This characteristic starting of the depressant action, first in the highest centres and later in the lower ones, occurs also in the higher animals.

The second stage of morphine action, the stage of tetanus, on the contrary, can be observed in its full development only in the cold-blooded animals, which, on account of their slight need of oxygen, can survive the cessation of the respiration. The increased reflex excitability first manifests itself in the frog by so-called spasmodic

respiration, groups of deep and rapid respirations being separated by long pauses. The spinal reflex excitability, which in the narcotic stage was so depressed and later paralyzed, returns again and is increased to such a degree that tactile stimuli excite tonic convulsions, just as is the case after strychnine. In principle, this second tetanic stage is indicated to some extent throughout the animal kingdom, but the higher the development of the central nervous system the more does this tetanic action fall in the background. If, however, dogs which have received large doses of morphine are kept alive by artificial respiration, a markedly increased reflex excitability of the cord can develop (*Lenhartz*). In man, too, abnormal reflex excitability may be observed after small doses, and in poisoning, especially in children, convulsions may occur. On the other hand, in the lower vertebrates the narcotic action is far less evident, morphine acting in fishes purely as an excitant like strychnine, without producing any preliminary depressing action.

In the more highly developed animals, the development of the morphine action does not take place so diagrammatically as in the frog. Above all, among the different species, there are not only differences in susceptibility to the drug, but also qualitative differences in the reaction of the nervous system to morphine. After administration of this drug to dogs, almost always salivation, retching, vomiting, and defecation occur. After some restlessness at the start, a quieting effect is noted, and then the animals sleep for hours. When large doses have been administered, increased reflexes and twitching of the muscles may be noted. With rabbits, rats, mice, and birds, narcosis is induced, but with cats, horses, and cattle, the drug causes great restlessness and a tendency to motor activity, with staggering and convulsions, but never a true narcosis (*Fröhner, Hess*). Contraction of the pupils occurs, as a rule, in those species which are narcotized by the drug, and dilatation in those which are excited.

This difference in the reaction to morphine, observed in different animal species, is of interest because in certain especially predisposed human beings morphine may excite instead of quieting the cerebral functions. In most human beings, however, a general sedative effect and desire for sleep result from doses of from 0.01 to 0.02 gm., while, after toxic doses, drowsiness and sleep are gradually succeeded by a state of profound unconsciousness.

The most important action of small doses of morphine is the depression of the ability to perceive pain. In the dog there results a stage of stupor and unwillingness to move, and the power of pain perception is almost entirely lost, although the ordinary sensory perception is hardly affected, nor is there any tendency to fall asleep. The motor regions of the cortex remain excitable even in deep narcosis. *Hitzig* observed no diminution of their susceptibility to electric stimulation, even after large doses. In fact, with moderate doses such

stimulation was more regularly followed by a motor effect than under normal conditions, although painful procedures (*e.g.*, twisting the dura) no longer caused whining or struggling, although the corneal and other reflexes were still present.

In man also the perception of pain is depressed long before the sensorium is affected. Formerly it was believed that this was due to a peripheral action of morphine on the peripheral sensory organs, but careful investigation of the condition of the algesic and the tactile senses has shown that morphine causes no diminution of the sensibility of the peripheral sensory organs, for the site of injection is no less sensitive than the corresponding part on the other side of the body (*Jolly u. Hilsmann*). We are dealing, therefore, with a central hypalgesia.

WITH NO OTHER DRUG CAN SUCH AN ISOLATED ACTION ON THE PAIN-PERCEIVING CENTRES BE SECURED, ALTHOUGH A SOMEWHAT SIMILAR EFFECT, BUT A SLIGHTER ONE, IS PRODUCED BY DRUGS OF THE ANTIPYRINE GROUP.

Doses as small as 5 mg. of morphine hydrochloride are sufficient to lessen perception of pain in adult patients who have not become accustomed to the drug. On the other hand, 0.01 gm. is not enough to produce an hypnotic effect in all individuals. Ordinary disagreeable sensations, as those of fatigue, hunger, or discomfort, as well as pain, are relieved by morphine, euphoria resulting, and herein lies the great danger of habituation to its use. A closer psychophysical analysis of these phenomena has demonstrated that the perception of stimuli from without is not at all depressed by small doses of morphine, but is, on the contrary, distinctly favored (*Kräpelin*). This stimulation of certain mental processes, which in normal individuals reaches its full development about half an hour after administration of 0.01 gm. of morphine, explains the ability of morphine habitués to do hard mental work so long as the morphine is acting. Other psychical processes, in which the accomplishment of a motor reaction plays a prominent part, as, for example, the performance of a muscular reaction after a given stimulation, are from the start retarded by morphine. This interference with motor processes is responsible for the quietness which develops after morphine long before somnolence does, and also for the tendency to dream peacefully and quietly, which is so characteristic of opium intoxication and which contrasts so strongly with the condition produced by alcohol.

Besides the above-mentioned depression of the central perception of pain which is the chief indication for the use of morphine, this drug exerts a similar ELECTIVE ACTION ON THE RESPIRATORY CENTRE, the respirations being rendered quieter, deeper, and slower by small doses. This will be more fully discussed later (p. 337 ff.).

The quieting effect exerted by morphine on intestinal peristalsis, which occurs when the drug is used for relief of pain or cough, may

be considered as a side action in so far as it is an undesired one, leading to constipation.

A number of other side actions may be considered from a common point of view, as they depend on the depression of certain central inhibitions which lessen the tone of the oculomotorius and the vagus centres, which inhibitions are in part removed by the action of morphine just as is the case during normal sleep.

Among these are the contraction of the pupil and the narrowing of the cleft between the lids (compare section on pharmacology of the eyes) and the increased tone of the vagus centre which causes slowing of the heart, which, however, occurs only after unusually large doses. Of similar origin is the spasmodic contraction of the bladder sphincter, which is in part the result of a central interference with its sympathetic nervous inhibition and which in human beings may prevent micturition in spite of a strong desire. In guinea-pigs this particular effect may be so pronounced that at times rupture of the bladder and death ensue (*Tappeiner*).

The NARROWING OF THE PUPIL is of diagnostic importance. It is certainly not the result of a local action, for it does not result when a morphine solution is dropped into the eye. This myosis is, however, characteristic only of the narcotic stage, and is succeeded by dilatation when the tetanic stage develops. As above mentioned, it does not occur in those animals whose higher centres are excited by morphine, for in them the pupils are dilated. Finally, in the last stages of morphine poisoning, the asphyxia causes mydriasis. It follows, therefore, that, although the pupils are usually contracted when morphine has been taken, the absence of this symptom in no way excludes morphine poisoning.

After small doses VOMITING seldom occurs, and then only in especially susceptible individuals, and small doses of atropine (0.2 mg.), as a rule, will prevent it entirely. After large doses nausea and vomiting are very commonly the initial symptoms of the poisoning.

The CIRCULATION is, generally speaking, but slightly affected by morphine. In man a passing acceleration of the pulse is followed by moderate retardation. In the dog, on the other hand, the slowing of the pulse is very pronounced and is due to augmentation of the central vagus tone. In other particulars in morphine poisoning the circulation suffers only secondarily as a result of a depression of the heart from the asphyxia and of a paralysis of the vasomotor centres. On the other hand, the depression of the respiration is very pronounced from the start and colors the whole picture.

ACUTE MORPHINE POISONING.—Toxic doses range from 0.03–0.05 gm. of morphine hydrochlorate, 0.2 gm. being the minimum lethal dose for adults, while 0.3–0.4 gm. may be considered as the average lethal dose for individuals unaccustomed to its use. Poisoning is usually the result of taking the drug by mistake or of errors in pre-

scribing or compounding or when the drug is taken with suicidal intent. Three-quarters of all the cases of morphine or opium poisoning occur in children under five years of age, which fact is explained by the great susceptibility of children to this drug. In small children even the administration of decoctions of dried unripe poppy heads as soothing potions may cause poisoning. Furthermore, inasmuch as morphine is excreted in the milk, poisoning of nursing infants may result from the consumption of morphine by the wet-nurse. On the other hand, the fœtus in utero is very resistant to morphine, as it does not breathe on its own account, and consequently the administration of this drug during pregnancy carries little risk, except that, when administered shortly before delivery, it may jeopardize respiration of the child after birth.

In morphine poisoning a condition of deep coma developing in the course of 15–30 minutes is characteristic. Large doses cause a deep sleep which at the start may be effectively combated by the application of external stimuli, but gradually the tendency to sleep is irresistible, and the patient passes into a condition of coma in which his response to sensory stimulation progressively becomes more faulty and finally complete unconsciousness and deep coma develop. The respiration gradually becomes more and more infrequent, irregular, interrupted, and rattling, and the skin becomes pale and cold, and the face cyanotic, but the pulse continues of good force for a long time. Finally all reflexes disappear, the infrequent respirations grow progressively more shallow, outspoken Cheyne-Stokes respiration often occurring, and death occurs as a result of the cessation of breathing, and, as the vasomotor centres also are paralyzed, the blood-pressure and the temperature of the body fall markedly. As a rule, the pupils remain contracted to the end, while sometimes death is preceded by convulsions. In less severe cases the coma may pass off, but often the patients, after a temporary improvement, sink back again into a comatose condition. When recovery occurs, constipation and difficulty in urination persist for some time after the patient has recovered from the deep sleep, which may last for a day or longer.

Treatment.—In connection with the treatment of acute morphine poisoning it is especially important to remember that, although vomiting almost always occurs spontaneously before the coma develops, the excitability of the vomiting centre is so rapidly depressed as the narcosis develops that emetics cannot cause vomiting. Consequently, in cases of poisoning by morphine or opium, it is essential that stomach lavage be practised for the purpose of removing any of the poison not yet absorbed. Inasmuch as morphine after absorption from the stomach, or when administered subcutaneously, is excreted again into the stomach, morphine may be found there even 15 or 18 hours after its administration, and therefore lavage should be practised even many hours after the administration of the drug. This holds good

also for cases in which the drug has been administered subcutaneously. As the drug is also excreted into the intestine, the attempt should be made to empty the bowels by cathartics and enemata. Attempts to render unabsorbed portions of the morphine insoluble by administering tannic acid produce but slight effects. On the other hand, it is possible to destroy morphine in the stomach by lavage with 0.4 per mille solution of potassium permanganate or by the administration of about 0.1 gm. of this salt.

In addition to these measures, the treatment is symptomatic, having as its objects the prevention of the deepening of the comatose condition and above all the prevention of the threatening cessation of respiration. For this reason the attempt is made to keep the patient awake until the sleep becomes so deep as to render this impossible. For this purpose one leads him about, applies various stimuli to the skin, and administers drugs which stimulate the central nervous system, such as camphor, black coffee, etc. If, in spite of such effects, the coma deepens, subcutaneous injections are made of atropine, our most powerful chemical stimulant for the respiratory centre. This antidotal treatment has proved itself to be life saving in many cases of poisoning in human beings, if the dosage of atropine is correctly determined, and similar results have been obtained in experiments on animals. The maximum dose should be injected and frequently repeated, the behavior of the respiration serving as a guide.

Therapeutic Uses.—As a means of relieving pain morphine can be replaced by no other drug. The ordinary dosage ranges from 0.003–0.03 gm. per dose, 0.1 gm. per day being the maximal dose under ordinary conditions. The detailed discussion of its field of usefulness in various internal and surgical diseases, especially in the treatment of different types of colic, neuralgias, etc., belongs to the clinician. No physician would be willing to do without this most valuable of all means of giving relief in painful conditions of an acute nature, or in those hopeless chronic cases in whom even the danger of acquiring the morphine habit must be looked upon as the lesser evil. As is well known, however, this danger must never be forgotten, for, in addition to blunting the perception of pain, morphine produces a condition of euphoria which carries with it the temptation to a chronic abuse of the drug even after the original occasion for its use has disappeared. The subcutaneous injection (introduced in 1855 by the American, Wood) of from ½ to 1 c.c. of a 1 to 2 per cent. solution is the best means of securing rapid relief of pain. Frequently about 0.2 mg. of atropine sulphate is added to such injections. It should be remembered, however, that it is particularly this form of administering morphine which opens the path to the development of morphine habituation, and consequently it is most necessary that the physician should exercise caution in thus administering the drug.

Another indication for the use of morphine is for the relief of a COUGH or of CARDIAC DYSPNŒA. The significance and importance of this sedative action on the respiratory centre will be further discussed in another connection (see p. 337).

In the treatment of SLEEPLESSNESS morphine is not so valuable as the hypnotics of the alcohol group in all those cases in which sleep is prevented by psychic excitement or nervous restlessness. Morphine should be used as an hypnotic only when pain, coughing, or dyspnœa prevents the falling asleep. Somewhat larger doses of morphine may be used, however, for the relief of conditions of motor excitement in the insane and in cases of poisoning by substances which cause cerebral excitement. Among such delirium tremens and poisoning by atropine are especially to be mentioned.

OPIUM.—Where it is desirable to have the effects of morphine develop somewhat more slowly or where the local effect on the alimentary canal is the desideratum, it is the general rule to make use of the galenic preparations. Opium itself, containing from 12 to 12½ per cent. of morphine, is used in dosage of from 0.02 to 0.1 gm., 0.15 and 0.5 gm. being the maximal single and 24-hour doses. The extracts containing 20 per cent. of morphine are to be used in somewhat smaller doses. Dover's powder (opium 1, ipecac 1, sugar of milk 8), the tincture, and the deodorized tincture, each containing 10 per cent. of opium, and the camphorated tincture, containing .4 per cent. of opium, are the more commonly used preparations.

The OTHER ALKALOIDS present in opium (see p. 30) have been but little investigated, particularly in respect to their actions in man. Narcotine, which after morphine is the one present in largest quantities, certainly has little pharmacological action, while the others, which are present in smaller quantities, all show a far weaker narcotic action than morphine. On the other hand, they all exert a much more pronounced stimulating action on the spinal cord, so that many of them, when given in toxic doses, produce convulsions of spinal origin which are not preceded by any narcotic action on the cerebrum similar to that produced by morphine (*v. Schröder*). The respiratory centre is also stimulated by some of these alkaloids. Consequently the mixture of all of the opium alkaloids produces a weaker narcotic action and less sedative effects on the respiratory centre than the morphine contained in it when given by itself (*Wertheimer-Raffalowich, Löwi, Bergien*). Clinical experience on human beings appears, however, to indicate that the mixture of all the opium alkaloids is as efficient for the relief of pain as is pure morphine in corresponding amounts.

Sahli has recently recommended, under the name of PANTOPON, a mixture of the hydrochlorates of all the opium alkaloids, which is soluble in water, claiming that with it one can obtain the effects of morphine modified by the actions of these other alkaloids. It is essentially a preparation of opium from which the useless constituents

have been removed and which may be injected subcutaneously. It contains the same alkaloids in the same relative proportions as does opium, but in about fivefold concentration, so that 0.02 gm. of pantopon corresponds to about 0.1 gm. morphine hydrochlorate.

CODEINE.—If in morphine the hydrogen of the alcohol hydroxyl group is replaced by alkyl radicals, the so-called codeines are obtained. The most important of these, the methyl ester of morphine, codeine itself, is present in opium in the small proportion of about 0.1 per cent. Under the trade names of dionin and peronin, the methyl ester and benzoyl ester have been introduced into use. The codeines differ from morphine principally in the fact that the action on the respiratory centre persists while the narcotic action on the higher cerebral centres is markedly diminished. According to *v. Schröder,* the power of increasing the reflex excitability of the cord is increased. These drugs are valuable substitutes for morphine in the treatment of coughs.

In the last few decades codeine has acquired a constantly increasing importance in the treatment of coughs. It is now manufactured synthetically from morphine, and is consequently much cheaper than when it had to be prepared from opium. It occurs in the form of colorless crystals, soluble with difficulty in water, and forming readily crystallizable salts, of which the readily soluble phosphate is the best for therapeutical use.

In man, 0.03–0.06 gm. of codeine produces about the same effects in relieving cough as 0.005–0.01 gm. of morphine, while it is about 20 times less poisonous. Therapeutic doses also produce some quieting effect, but even large doses do not cause actual narcosis. On the contrary, in the relatively rare cases of idiosyncrasy only restlessness and slight muscle twitchings and mydriasis have been observed. In animal experiments the narcotic actions on the cerebrum are so slightly expressed that the older investigators overlooked them when moderate doses were administered, while after larger doses its property of causing tetanus is alone evident.

Codeine, therefore, may be looked upon as a very mildly acting morphine. By its use in place of morphine the danger of the development of the habit may be avoided in cases of chronic coughs. It appears to be less suitable as a means of relieving pain or as a general sedative, and should be used for such purposes as a substitute for morphine only in children.

The ethyl ester of morphine, DIONIN, closely resembles codeine. On the other hand, diacetyl morphine, obtained by the substitution of acetic acid radicals for the hydrogen of both of the hydroxyl groups of morphine, and known as HEROIN, possesses a far more powerful pharmacological action. Even in doses of a few milligrammes it exerts a sedative action on the respiratory centre, but in laboratory experiments even comparatively small doses produce dangerous toxic effects

on the medullary centres. The dose of dionin ranges from 0.03–0.05 gm. per dose and that of heroin from 0.003–0.005 gm. (!) per dose. In judging of the value of these substitutes for morphine, the most important point to determine is the degree in which they may cause habituation similar to that caused by morphine.

Morphinism.—This brings us to a discussion of the most serious harmful effect of morphine and opium, the development of chronic morphinismus when the drug is continually administered. When morphine is chronically misused, it is taken not only for the purpose of relieving pain or coughs, but the patient takes it just as soon as he feels tired or uncomfortable, and, when it is thus repeatedly taken, habituation gradually develops so that the dose must be increased in order to obtain the same effects. If the habit has thus been acquired, as soon as there is an interruption of its regular administration "abstinence" symptoms develop, and the patient suffers from a general feeling of distress and becomes restless and consequently has recourse all the oftener to the drug in order that he may again be quieted and able to perform mental tasks. The rapidity with which the dose must be increased varies in different individuals, and the daily consumption of one or two grammes of morphine by a morphinist or even as much as four grammes is no great rarity. Sooner or later, depending on the individual resistance, the consumption of such amounts leads to serious psychical disorders and to disturbances in the functions of all the organs. The skin becomes dry and rough, but at times there is a tendency to profuse sweating. The digestive apparatus in particular suffers seriously, catarrh of the stomach and intestines, constipation, diarrhœa, etc., developing. Emaciation and anæmia, often accompanied by albuminuria and glycosuria, are among the other harmful effects of this habit. When the attempt is made to withdraw the drug, severe "abstinence" symptoms appear, and the patient suffers from restlessness and sleeplessness, from depression accompanied by a feeling of anxiety, or he may become extremely excited, or nausea and diarrhœa or even collapse may complicate the picture.

It is the euphoria which accompanies the therapeutic effects of morphine which makes it so easy to acquire the habit. Consequently the danger is not so great when those substitutes for morphine are used in which the specific effect on the cerebrum is less well developed, for then there is no such temptation to increase the dose over that which produces the desired therapeutic effects. As codeine and dionin do not produce any euphoria, their use is not followed by their abuse, but, when heroin has been used repeatedly, serious habituation has been observed to result.

Causes of Tolerance to Morphine.—The partial explanation of the true cause of habituation—*i.e.*, an explanation of the reason why it is necessary constantly to increase the dose in order to obtain the

usual effects—has been furnished by the investigations of *Faust*, who found that this is closely related with the fate in the body of morphine and its congeners.

Formerly much care was taken to isolate morphine in unchanged, or more or less altered, form from the urine, but small amounts of the unchanged alkaloid may be found in the urine only when very large doses have been taken, and even altered morphine cannot be detected after any usual doses. On the other hand, *Marmé* found in dogs, and later *Alt* found in human beings, that morphine injected subcutaneously was excreted unchanged into the stomach. This excretion begins a few minutes after the injection and persists as long as do the effects of the morphine. Using more exact quantitative methods, *Tauber* found in the fæces about 41 per cent. of the morphine which had been injected in the course of 10 days.

The condition of the mucous membranes of the alimentary canal exerts considerable influence on the excretion of morphine, hyperæmia and increased secretion of the epithelium favoring it. By the local action of alcohol or of the irritating decoctions of soap bark or of senega root on the alimentary canal, *McCrudden* was able to increase the amount of morphine excreted in the fæces from 44–47 per cent. to 58–64 per cent. of the amount which had been subcutaneously injected each day. His results suggest that in morphine poisoning the elimination of the drug could be favored by the administration of such drugs, just as the attempt is made, by increasing the diuresis, to influence the elimination of those poisons which are excreted in the urine.

In *Faust's* investigation of the causes of habituation, he was able to demonstrate that, when a single injection of morphine is given, dogs excrete, through the stomach and intestines, about 70 per cent. of the amount administered; he also found that, when each day progressively larger doses are injected, the amount of morphine excreted in the fæces decreases, so that finally, in spite of the daily injection of ordinarily lethal doses, no morphine appears in the excretions. Inasmuch as after death the organs of these animals contain only very small quantities of the poison, *Faust* was justified in concluding that, when habituated to morphine, the organism acquires the power of destroying much larger amounts of this drug than an individual not accustomed to its use. On the other hand, according to *Bouma*, when codeine is repeatedly administered, there develops neither any pronounced insusceptibility to increasing doses nor any increased power of destroying the drug.

The results of these investigations have thus made clear one of the causes of tolerance, but it is not probable that this is the essential and most important cause for the insusceptibility of the morphinist. Such individuals exhibit their insusceptibility to large doses of morphine especially when these are administered subcutaneously,—that is, in a manner which favors the very rapid absorption and the rapid arrival of the morphine in the central nervous system. In order to explain, by an exaggerated or increased power of destruction, the tolerance to such amounts of poison as circulate around in the body in the first short period following its injection, it would be necessary to assume that the poison is very rapidly destroyed. The experiments of *Rübsamen* with rats habituated to morphine have furnished the necessary data to determine this point. He was able to render these

animals tolerant to doses twice as large as the usual lethal dose. When he determined how much morphine was still present in the body of such immunized animals at a time when symptoms of the poisoning would be at their height in unhabituated rats, he found that it was still possible to isolate from the body an amount of the unchanged poison which would have produced severe symptoms of poisoning in animals which had not been habituated to this drug. The animals which had previously received numerous injections of morphine, however, showed hardly any symptoms worth mentioning.

From these findings the conclusion must be drawn that the repeated administration of morphine results in the development of a lessened susceptibility on the part of the cells. Against this conclusion only one criticism may be urged,—namely, that it is possible that the central nervous system acquires in a particularly high degree an increased power of destroying morphine so that it is not possible for the poison to reach the particularly susceptible nervous elements in a sufficiently high concentration. Special experiments, not yet published, which were undertaken to investigate this point have failed to give any evidence that the brains of immunized animals exhibit any such increased power of destroying morphine.

However, there is an undeniable connection between habituation to and the more rapid destruction of certain poisons in the organism which has become insusceptible to their toxic actions. In the case of certain other drugs such a connection can be demonstrated (*Flury*). Thus, *Pringsheim* has shown that alcohol when administered daily is combusted more rapidly than when given but once. However, in the case of alcohol there is no doubt that a diminished cellular susceptibility develops, for, as is well known, the alcoholic exhibits an increased resistance to the action of ether, which in its pharmacological actions closely resembles alcohol, in spite of the fact that ether is not at all combusted in the organism but is excreted unchanged.

Opiophagia, or opium eating, is quite analogous to morphinism. The abuse of this drug has spread from India over the whole of Asia and Turkey,—in Persia and in Turkey, in the form of opium eating, in China and in all lands whither the Chinese have immigrated, in the form of opium smoking. In this latter form of indulgence, for which in China opium extracts prepared in a special manner are used, undoubtedly a portion of the morphine passes over into smoke, but a large portion is destroyed, and consequently the harmful effects of opium smoking do not develop so rapidly as in opium eating. In both cases, however, in the course of time the symptoms of a chronic intoxication develop which closely resemble those of morphine (*v. Bibra*).

Hashisch.—In former times various hemp preparations were widely used as substitutes for morphine. Under the name of hashisch, extracts of the resin of Indian hemp, Cannabis Indica, are used as a stimulant throughout the Orient, especially in Egypt and in India as also in Turkey. The great instability of its active principle, which has recently been isolated in pure form by *S. Fränkel*, explains why various personal experiments which have been made in Europe have not always given such typical results as would be expected, judging by the descriptions of hashisch intoxication in the Oriental. The condition of intoxication produced by hashisch differs from that resulting from the action

of morphine in the predominance of pleasant hallucinations and active motor restlessness. In experiments on animals, on the other hand, *Fränkel* found that the cannabinol caused only narcosis and a condition of catalepsy.

Morphine and Scopolamine.—The exaggeration of the effects of small doses of morphine which result from its combination with scopolamine are of great practical importance. This synergism may be experimentally demonstrated in various species of animals, especially in those species in which scopolamine alone, even when given in large amounts, produces no narcotic effects. The combined administration of small doses of morphine and small doses of scopolamine, which by themselves produce hardly any effects, results essentially in an exaggeration of the effects of the morphine (*Bürgi, Madelung*). Morphine and the hypnotics of the alcohol group when administered simultaneously also act synergistically, with a resulting exaggeration of each other's pharmacological actions (*Bürgi, Fühner*).

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ALCOHOL

The drugs of the morphine group, as we have learned, exert a preponderatingly depressing influence on the central nervous system of vertebrates and produce in invertebrates quite different effects and in vegetable organisms no effects at all.

The next group which we have to consider is a large and quite different one, consisting of substances whose actions, while preponderatingly depressing ones, are not confined to the central nervous system of vertebrates, but are exerted on all types of animal organisms and

affect not only nervous tissues but all living protoplasm. This is the GROUP OF ALCOHOL [spoken of also by various authors as the ALCOHOL-CHLOROFORM GROUP, the GROUP OF HYDROCARBON NARCOTICS, etc.—TR.] This somewhat arbitrarily named group includes, as a matter of fact, all indifferent organic carbon compounds which are soluble in fats, with the exception of such hydrocarbons as are not volatile and are entirely insoluble in water, and are consequently incapable of absorption by the organism. Among its members may be found simple and substituted hydrocarbons, alcohols, aldehydes, ketones, ethers, esters, acid amides, substituted ureas, and other types too numerous to mention.

Of this practically unlimited number of substances only a relatively few are actually employed as medicines, which are variously known as hypnotics or sedatives and as anæsthetics, according as their action is more or less pronounced or lasting or evanescent. Ethyl alcohol occupies an intermediate position between these two classes, connecting them and belonging, as it were, to both. Consequently its properties and actions should be discussed first of all.

ALCOHOL.—Ethyl alcohol, C_2H_5OH, is formed from sugar by yeast fermentation. When during the fermentation about 18 per cent. of alcohol has been formed, the fermentation ceases, but may be started up again by dilution with water. It is thus evident that even yeast cells are paralyzed by a certain concentration of alcohol in the surrounding fluid, and this power of alcohol to depress or paralyze functional activities is found to hold good for all forms of living organisms.

SYMPTOMS OF STIMULATION AFTER ALCOHOL.—Often, but by no means always, the depressing effect of a drug is preceded by a stimulating one, and it is desirable to determine whether or not this is also the case with alcohol. As a matter of fact, in man the first, and, at the start, the only noticeable effects produced by it, are exaggerated talkativeness and motor restlessness, quickened breathing and pulse, and flushing of the face, all apparently signs of stimulation, which are followed, only when larger amounts are consumed, by a general depression and a feeling of fatigue, and by slowed respiration and circulation, and diminution of all reflexes.

It has been demonstrated that the primary action, responsible for this apparent stimulation, occurs in the cerebral hemispheres, for the less the cerebral development of the animal the slighter are the appearances of stimulation, and, as *Baratynsky* showed in frogs and pigeons, which, though decerebrated, were kept alive for months, these do not occur at all if the cerebrum has been removed.

The nature of this excitement or stimulation has been the subject of much discussion. Before starting in on such discussion it is desirable that the SIGNIFICANCE OF STIMULATION be thoroughly understood.

Every expression of life, whether conscious or unconscious, is a

reaction,—*i.e.,* a response to a stimulus. It is impossible for any change, movement, or other functional activity in a living organism to occur spontaneously,—that is, without a sufficient cause. If any substance by its action in the body causes a reaction, there are three ways in which it can do so. It may do this: (1) by acting itself as a direct stimulus (as does NaCl when applied to nerves); (2) by making it possible for other constantly occurring but ordinarily subliminal stimuli to become efficient; or (3) by bringing it to pass that the discharge of energy which results from a given effective stimulus produces results which are more wide reaching or violent than usual. The first we call DIRECT STIMULATION, the others EXALTATION OF THE EXCITABILITY. The first may be compared to the closing of the quicksilver contact in an electric circuit, the second to the rendering the points of contact more delicate, and the third to the removal from the circuit of resistance coils or the interpolation of better conductors. It is evident that in the last two cases, which, by the way, usually cannot be differentiated from each other, we are dealing with an alteration in the functional condition of the physiological mechanism in question, which causes either an acceleration of the reaction or a removal of inhibition.

We must look on all the functional activities of cells as resulting from chemical processes, either katabolic (disintegrative) or anabolic (constructive or synthetic) in nature, the former accompanied by a discharge of energy, the latter leading to its reaccumulation. These reactions in the cells may be accelerated by catalyzing agents or retarded by inhibiting ones, in a fashion quite analogous to that in which chemical reactions may be modified by appropriate agents. Increased discharge of energy—that is to say, increased functional activity, or STIMULATION—RESULTS ALIKE FROM THE REMOVAL OF INHIBITING FORCES OR THE INTRODUCTION OF ACCELERATING ONES.

THE REMOVAL OF INHIBITION is perhaps the more common phenomenon, for in the majority or perhaps in all organs the functions are in a state of balance or rivalry, each function normally being limited or inhibited by an antagonistic one. The elimination, by depression or paralysis, of any function thus results in the initiation or augmentation of the activity of the corresponding antagonistic one. This connection, moreover, obtains not only between antagonistic functions but also between those which produce similar effects and which, as it were, compete with each other. For example, the elimination of the cardiac vagus of one side causes an augmentation in the excitability of that of the other side, this indicating apparently that there is a certain competition between the influences exerted on the peripheral cardio-inhibitory organs by the vagi of the two sides (*v. Tschermak*). In a similar fashion centrifugal stimuli compete in the terminal nervous organs with chemical stimuli which act in the periphery. Thus the excitability by chemical agents of the peripheral dilator mechanism of the cat's iris is augmented by section of the cervical sympathetic, which is the ordinary path for impulses coming from the centre to this organ.

With *Goltz* and *J. Loeb* we attribute to the cerebrum the functions of inhibition and exclusion, which alone render possible the concen-

tration of the attention and will on the acts of perception or motion needed at the time, without regard to all other centripetal or centrifugal processes in the central nervous system. It seems plausible, then, to assume that *the early effects of alcohol are limited to a weakening of this inhibiting function of the cerebrum,* while the lower portions of the central nervous system are not directly influenced by it. As a result of this removal of inhibition, we see the evidence of their exaggerated activity in the tipsy individual's unrestrained behavior, his loquacity, his tendency to laugh or weep without cause or to burst into a tempest of rage. As in certain cases of bilateral disease of the cortex analogous symptoms occur, it would appear that the above assumption satisfactorily explains such symptoms. In the same way the faulty control of equilibrium and the loss of muscle sense in intoxication indicate a direct depression of the cerebellar functions. However, it cannot be absolutely denied that a *direct stimulating action* is exerted by alcohol on the basal ganglia and on certain centres in the medulla, and that this plays an important part here, especially in connection with the symptoms of stimulation of the motor portions of the brain.

Motor Excitement.—It is well known that symptoms of motor excitement result from the administration of alcohol, and it is to these effects that it owes its reputation as a reviving and strengthening agent, of which use is gladly made in cases of fatigue or bodily weakness or to aid in the performance of heavy tasks. It is only in the last decades that an exact and complete proof has been brought that alcohol actually does cause such motor excitation. *W. Lombard,* using Mosso's ergograph, was able to show that, when small quantities of alcohol were taken, the power of performing voluntary muscular work was not directly increased, but the development of the feeling of fatigue was postponed, so that more voluntary work was performed by the muscles. This, however, is not due to an increase in the capacity of the muscles, for, when involuntary muscular contractions were produced by peripheral electric stimulation, alcohol lessened the capacity for muscular work. *From these results it is clear that the increase in capacity for work is central in its causation and is purely the result of retardation of the development of the sensation of fatigue. Frey, Kräpelin*[1] *and his collaborators,* and *Joteyko* have confirmed these observations, but *Rivers* was not able to do so. *Kräpelin's*[3] physiological discussion and *Joteyko's* very plausible explanation of the ergographic records, which is based on a mathematical analysis, both indicate that a facilitation of the cerebral motor processes is involved in these results (see Pharmacology of the Muscles, p. 422).

As this facilitation of the motor processes can be brought about as often as wished by repeating the administration of small amounts of alcohol, *Kräpelin* assumes it to be the result of a direct but very temporary exaltation in the excitability of the motor tracts and not the result of a temporary weakening

of inhibition. However, this argument is not convincing, for a temporary depression of the inhibitory centres by alcohol may be assumed just as readily as a temporary excitation of the motor ones, and therefore it could just as well be repeatedly induced.

Still less valid is the opposing view that the direct action of alcohol is always a depressing one, and that the "stimulation" produced by it is only an apparent one, due only and always to depression of inhibition or disturbance of the normal balance in the cerebrum, etc. As a matter of fact, it has been shown that alcohol does produce a direct augmentation of the excitability in isolated frog's nerves (*Mommsen, Efron, Breyer*), in nerve-muscle preparations (*Scheffer* and others), in ciliated epithelium (*Engelmann*, 1868; *Breyer*, 1903), and also in plant cells, in which alcohol accelerates the flow of plasma (*E. Josing*). All of this being so, it is hard to see why it should not cause similar stimulation of central nervous organs also. Apparently it is largely a question of terminology, for the utilization of current in an electric circuit may be increased just as well by lessening the resistance, by shortening the circuit, or by cutting out a portion of it, as by improving a portion of the conducting path, and, whether the conduction is improved and the resistance thus lessened or whether the conduction for a competing or antagonistic current be lessened, the result is the same, for it is always a question simply of supplying greater current energy through the excited segment and not of the production of energy.

The "STIMULATION" from a single dose of alcohol is never of long duration, lasting only for 30 to 60 minutes, and with larger amounts it is quickly followed by depression. For abstemious adults the limits for such "stimulating" doses may be placed at about 30–40 grammes of alcohol, corresponding to 250–500 c.c. of wine or a litre of beer. For those accustomed to the use of alcohol the dose must naturally be somewhat larger.

In addition to facilitating the performance of motor acts, alcohol also, especially in sickness or exhaustion, when such may be accomplished only by considerable effort of the will, produces a *feeling of increased strength and of general well-being.* Other physiological processes, such as those of nutrition and metabolism, may be indirectly influenced in a favorable sense by the improved nervous condition. In this way one phase of the analeptic, stimulating action of alcohol is sufficiently explained. Moreover, it is a well-known fact that when alcohol is taken frequently, there quickly develops a habituation to the effects produced on the nervous system, so that the stimulation felt at the start is no longer experienced unless the amounts taken are increased. Consequently it is clearly evident that the habitual daily use of alcohol is not only incapable of facilitating or improving the performance of physical work, but that, on the contrary (on account of its other harmful actions), it impairs it. The experience obtained in different wars and in sports is in complete accordance with this view.

RESPIRATION.—The other side of the stimulating action of alcohol, in so far as the central nervous system is concerned, deals with its effects on the respiration. This is strengthened so that the respiratory volume—*i.e.*, the amount of air respired in a unit of time—is increased. This is due not only to REFLEX STIMULATION through the senses of taste and smell and from the bronchial and stomach nerves,

or to increased muscular activity, but probably also to a DIRECT STIMULATION of the respiratory centre (*Wilmanns* and others). This strengthening of the respiration occurs even in sleep and after doses which cause sleep, and consequently this action may be of value clinically in cases of poisoning or shock. However, the more volatile members of the alcohol group (ether, acetic ether, etc.) are in this respect more efficient and useful. It goes without saying that such an artificial strengthening of the respiration can be of no value to healthy hard-working men.

EFFECTS ON THE POWERS OF PERCEPTION AND ASSOCIATION.—As far as has been shown up to the present, most of the functions of the central nervous system are depressed by alcohol. This is especially so for the faculties of perception and association. This is evident from the general experience that judgment is never improved by alcoholic indulgence, but is always impaired, and the exactly conducted psychological studies of *Kräpelin*[1,3] and his collaborators led them to the same conclusions.

EFFECTS ON THE MOOD.—The sensation of physical and psychical well-being is determined by the intensity of the feelings of discomfort and by the intensity of the inhibitions, under whose constantly varying influence we exist, for positive feelings of pleasure can never be consciously experienced except for the time being and, according to the law of *Weber* and *Fechner,* must consequently disappear if the stimuli remain the same. The feeling of health in a similar fashion means nothing else than the failure to be conscious of any pathological disturbance. From this it necessarily follows that any general blunting of the perception and conception of life must lead to an euphoria, and if, in every-day life, "wine makes glad the heart of man," it is self-evident that this must be even more true for an invalid suffering in body and soul. *As a matter of experience, almost all the functions of the body, the appetite, and, depending on it, the digestion, the metabolism, the circulation, the respiration, and the ability to sleep, are very markedly affected by the general subjective condition,—i.e., by the intensity of the subjective euphoria. Therefore, it is evident that, in proper cases, alcohol may be a very valuable medicament for the preservation and augmentation of the strength of the invalid.*

However, it is important to emphasize the fact that in many nervous patients any amounts of alcohol, even very moderate ones, can produce harmful effects. This is the case, among others, with epileptics, whose condition of depression in many particulars resembles that caused by alcoholic intoxication, and may be most strikingly aggravated as a result of the consumption of alcohol (*Kräpelin*[2]). Moreover, it should not be forgotten that grave harm may result from advising long-continued or regular use of alcohol for the purpose of strengthening a patient, or of stimulating his appetite and calming his nerves, and that, under all circumstances, this is particularly

dangerous advice to give to neurasthenic patients in whom the will power is weak.

Large doses of alcohol cause blunting and complete paralysis of the functional activity of the cerebrum. The consciousness and the cerebral reflexes are abolished. The centres for the regulation of heat and the spinal centres are paralyzed, and finally, when fatal doses have been given, the excitability of the respiratory centre in the medulla is completely abolished. Therapeutically this narcotic action of alcohol may be utilized in the symptomatic treatment of conditions of excessive excitability of the reflex centres, as, for example, in strychnine poisoning. This is especially the case if other, perhaps more appropriate, remedies are not at hand. It is also of some interest that some savage races are accustomed to intoxicate to a state of complete insensibility (*Felkin*), with palm wine or other alcoholic beverages, any one about to be operated upon, and under certain conditions this could be done, in case of need, even in civilized lands. However, it is impossible to estimate beforehand, with any certainty, the duration of the primary stage of excitement or that of the complete narcosis with abolition of the reflexes. In addition to this decided disadvantage, the use of alcohol as an anæsthetic possesses also the disadvantage that it is followed by long-continued extremely disagreeable after effects.*

Circulation.—Inasmuch as alcohol, as has already been mentioned, exerts its action not only on the nervous tissues but also on all living protoplasm, in man its effects are not limited to those on the functions of the central nervous system, but are exerted with greater or lesser intensity on the functions of all organs. At this time these will be discussed only in so far as appears necessary to secure a proper understanding of its greatest action. A part of this is a strengthening of the cardiac action and an acceleration of the pulse, which in health occurs to but a slight degree or not at all, but which in disease is often manifested in a very useful and striking fashion (see pp. 258, 316).

Alcohol also depresses the tone of the vasomotor centres and thus dilates the vessels, particularly the cutaneous ones. The feeling of warmth, which is obtained by drinking alcohol when cold, depends on this dilatation of these vessels, for our sensations of warmth depend entirely on the condition of the terminal organs of the cutaneous temperature nerves. That is to say, the better the circulation in the skin the warmer we feel. Consequently, even small doses of alcohol, as a result of this dilation of the cutaneous vessels, produce a deceptive

* According to *Finkelnburg*, alcohol causes a rather lasting stimulation of the secretion of the liquor cerebri and consequently an increase in the subarachnoid pressure. It is not impossible that the post-alcoholic headache is due to this increase in intracranial pressure [for spinal puncture can often bring prompt and striking relief.—Tr.].

feeling of warmth, in spite of the fact that larger amounts of heat are lost by the body as a result of bringing heat from the interior of the body to the surface where it is given off.

After non-narcotic doses this greater LOSS OF HEAT is not compensated for by an increase in the production of heat, for after large doses the heat-regulating nerves, like the other cerebral centres, are depressed and the regulation by chemical means becomes inadequate, and consequently the temperature of the body is markedly lowered. This is an explanation of the danger of an intoxicated individual's freezing to death in winter. As will be more fully discussed in the section on antipyresis, the disturbance of the heat-regulating mechanism is especially pronounced in fever, and in former times alcohol was used as an antipyretic. As a matter of fact, its thermic action is in principle not at all different from that of the true antipyretics, but it is developed only after doses which produce marked effects on other functions. Consequently, alcohol should not be used as a specific antipyretic, any more than arsenic should be used as an emetic although its emetic action is entirely similar to that of antimony.

ANTISEPTIC ACTION.—As a result of certain clinical observations, the claim has been made that alcohol can exert antiseptic and bactericidal actions after it has been absorbed into the blood; but this assumption has no valid foundation. As far as it is possible to draw any conclusions from the experimental observations of *Laitinen*, it, on the contrary, diminishes the resistance to bacterial infection. That, however, patients with septic fever can support very unusually large amounts of alcohol without becoming intoxicated is a noteworthy fact, which has been observed, and which may be explained in the same way as the unusually high resistance to morphine exhibited by dogs poisoned by atropine (*Binz*). It is also possible that in fever alcohol is combusted more rapidly than in health, but thus far this has not been investigated.

Externally, however, on account of its solubility in fat and water, and on account of its power of hardening the tissues, alcohol may be advantageously used as a disinfectant (*Ahlfeld*). On account of these same properties, when alcohol is rubbed on the skin it penetrates the epithelium and causes a local irritation of sensory and vasodilator nerve-endings and may be used as a counterirritant.

THE FATE OF ALCOHOL IN THE BODY.—Alcohol, with the exception of slight traces (2–5 per cent.) which leave the body through the lungs, is completely burned in the bodies of warm-blooded animals, self-evidently with a corresponding production of heat. According to *Pringsheim*, animals accustomed to alcohol combust it more rapidly than the unhabituated controls, its combustion taking place in about two-thirds of the time which is necessary for the combustion of similar doses when administered to the controls.

It has been established by numerous investigators (*Atwater, R. O.*

Neumann, Rosemann, and others) that CALORICALLY EQUIVALENT AMOUNTS OF THE CARBOHYDRATES AND FATS OF THE BODY MAY BE PROTECTED FROM COMBUSTION BY THE METABOLIC COMBUSTION OF ALCOHOL. Under certain circumstances it appears to be able to act as a physiological substitute for the carbohydrates, aside from the utilization of its caloric energy value, a fact which appears not without importance. In diabetic acidosis the administration of alcohol, like that of carbohydrates, decreases the formation of acetone (*Neubauer*) [and also that of the pathologically more important oxybutyric acid.—TR.]. Alcohol may therefore, in so far as its toxic side actions may be disregarded, be considered as a surrogate for food, and may occasionally be useful as such in the treatment of disease.

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GENERAL ANÆSTHETICS

While studying the action of alcohol on the central nervous system, we have at the same time been learning the typical effects of a very large number of other substances, of which the greater number belong to the aliphatic series. These are those hydrocarbons, alcohols, ethers, esters, etc., of an indifferent nature, possessing neither acid nor alkaline properties, nor those of the salts, and which are characterized less by their chemical than by their physical affinity for certain constituents of the protoplasm. Some other substances which do not belong to the aliphatic series—as, for example, nitrous oxide or carbon dioxide—also are to be considered as belonging pharmacologically to this great alcohol group. Naturally, though, of all this large army

of substances, only a few are practically useful in medicine,—namely, those whose narcotic action is relatively a pure one and at the same time sufficiently powerful.

However different, on superficial observation, may be the appearance of an ether narcosis, which is well developed but which lasts but a short time, from that of the merely calming but rather persistent effect of a small dose of sulphonal, in their nature the actions of these drugs are essentially similar, but in the two cases we utilize entirely different degrees or phases of an action which in principle is identical. In each case these substances, whether classed as hypnotics or anæsthetics, when given in large doses, by their depressing action abolish, for the time being, the functions of the brain and also those of the spinal cord, while the respiratory centre is still able to perform its functions satisfactorily and the circulation remains comparatively little affected. In anæsthesia produced by ether or chloroform, the fact that they are administered through the lungs makes it possible very accurately to induce that degree of their pharmacological action which is just this side of the danger line, and to maintain this condition only as long as appears necessary for the painless accomplishment of the operation. In contradistinction to this, when hypnotics are used, it is only the early stage of the general "alcohol" action which is utilized, during which stage the excitability of certain functional tracts in the cerebral cortex is depressed only to a slight degree.

Historical.—Medicine owes the discovery of general anæsthesia to experiments which were made to determine the effects of chemically pure gases on human beings. When, toward the end of the eighteenth century, the science of chemistry was occupying itself with various gaseous substances, the effects of these gases in human beings was frequently studied, and in fact the attempt was made to utilize these effects in the treatment of disease. The intoxicating effects of nitrous oxide were discovered early in the nineteenth century by the English physicist, *Humphry Davy,* who recognized that "among other properties nitrous oxide appears to possess the power of relieving pain," and he suggested that it could be advantageously used for surgical operations. However, the fact that the condition of intoxication observed was merely a forerunner of a true narcosis was not recognized by *Davy* or his contemporaries, perhaps because of the difficulty of handling the gas.

Consequently experiments with the inhalation of nitrous oxide went out of fashion, and were only now and then conducted for the purpose of demonstration, in spite of the fact that at the start they had been described with great enthusiasm and had been frequently repeated. It was due to such a demonstration in Hartford, Conn., that the dentist, *H. Wells,* in 1844, forty years after *Davy's* discovery, rediscovered nitrous oxide anæsthesia.

He noticed that one of the persons to whom this gas had been administered, after inhaling it staggered about in a somewhat intoxicated condition, and happening, while so doing, to receive a by no means slight injury, exhibited no signs of suffering. *Wells*, however, did not succeed in introducing nitrous oxide anæsthesia into practice, his endeavors to do so remaining fruitless on account of the difficulty with which the gas could be handled and because it was not suitable for major operations. It was only at a much later date that an improved technic permitted this method of anæsthesia to be widely adopted.

However, the idea of inducing anæsthesia by causing a gas to be inhaled was pursued further, with happier results, by an eye-witness of Wells's earlier experiment, *Morton*, a Boston dentist, who in coöperation with the chemist, *Jackson*, sought for some gas more suitable for this purpose. *Jackson* suggested that experiments be made with ether, whose intoxicating effects on human beings were already known, and which possibly some surgeons may have employed even before this time.

In 1846 in the Massachusetts General Hospital of Boston, *Morton* and the surgeon, *Warren*, performed the first major operation under ether. This discovery was communicated to the Academy in Paris in 1847, and in the same year *Flourens* also made the communication to the Academy, that, in experiments on animals, chloroform produced the same effect as ether, except that it anæsthetized them more deeply and more rapidly. In 1847 *Simpson* of Edinburgh made use of chloroform anæsthesia in human beings for the first time.

This most important step of progress was entirely due to the discovery of volatile narcotic substances, for no other path of absorption is so adapted for the rapid attainment, without danger to life, of that degree of pharmacological action adequate to produce anæsthesia, and at the same time so adapted to facilitate its rapid diminution at any chosen moment, as is the path of absorption through the lungs. All the narcotics administered by the stomach which had formerly been used for the induction of surgical anæsthesia (mandrake, opium, and alcohol) suffer from the disadvantage that their actions develop far more slowly and possess the even greater drawback that, when once the dose had been administered, one is entirely unable to prevent a further rise in the concentration of the drug in the blood if this be undesirable.

Volatility of Prime Importance for the Practical Use of General Anæsthetics.—For the rapid attainment of a complete anæsthesia, the most rapid path of absorption of the narcotic must be available, and it is equally important that its excretion shall also take place by an equally rapid route, in order that its concentration in the blood may at any time be altered as occasion arises. When ether and chloroform are used as anæsthetics, the interruption of its inhalation suffices immediately to transform the portal of entry for the narcotic into a most efficient organ of excretion.

The surprising rapidity with which volatile substances are absorbed from the lungs into the blood and pass out of the blood into the expired air is readily explained by the nature of the mechanism of the absorption of oxygen and excretion of CO_2 in the lungs. The

enormous surface of the pulmonary capillaries, from which the alveolar air is separated by a membrane composed of only one layer of cells, supplies all the conditions for the most rapid interchange of gases and vapors. However, this path is not available for all gases, for such vapors as chlorine or sulphurous acid, by their irritating effects, produce a spasm of the glottis and other reflexes in the upper air-passages so that the lungs are protected from them. Consequently, only such gases or vapors may be used as anæsthetics as are relatively non-irritating and consequently do not cause such defensive reactions to too great an extent, although they are clearly produced with a certain degree of intensity by chloroform and especially by ether.

GENERAL ANÆSTHESIA

Among the narcotic gases and vapors which may be inhaled and which meet the conditions necessary for their absorption through the lungs, ether and chloroform, and, especially for short operations, ethyl bromide, ethyl chloride, and nitrous oxide, are practically the only ones which need be considered. When properly administered, these all produce a condition of complete insensibility and unconsciousness, —a general anæsthesia. The term, "general anæsthesia," is used for this condition in contradistinction to that of local anæsthesia, in which the abolition of sensibility is obtained by the paralysis of the sensory nerve-endings at the seat of the operation.

In the induction of anæsthesia, before complete anæsthesia is induced the perception of impressions from without is abolished, so that, even at the time when consciousness is still preserved and is only somewhat clouded, painful procedures are hardly perceived at all, a condition of analgesia having been attained. When nitrous oxide anæsthesia is employed, as a rule, one does not go beyond this stage. In deep ether or chloroform anæsthesia, on the other hand, the consciousness is completely abolished and voluntary motions cease, just as in profound sleep. Under these conditions the lower portions of the cerebrum, the basal ganglia, etc., are put out of function, as it were, and later the spinal cord is similarly affected, so that the tone of the voluntary muscles is abolished and the operation is not disturbed by any reflex movements. Only respiration, circulation, the interchange of gases in the lungs, and the metabolism of the tissues remain approximately normal during the anæsthesia. The art of anæsthetization consists largely in preventing the extension of such effects to the respiratory and circulatory centres.

Ether (diethyl ether, $C_2H_5OC_2H_5$), also called sulphuric ether, on account of its manufacture by heating alcohol with sulphuric acid, is a clear, colorless fluid, with a peculiar smell and burning taste, which boils at 35° C. [U.S.P. 36–37° C.]. This low boiling point is of great importance, for it is the expression of its great volatility, which is of the greatest importance for its administration as an anæsthetic.

At ordinary temperatures the evaporation of ether occurs rapidly and is accompanied by well-marked loss of heat, so that it may produce a cooling to temperatures far below 0° C.

Ether is miscible with oils and alcohols in any proportions, and is soluble in water in the proportion of one part in 12 at 17° C., while one part of water is soluble in 35 parts of ether. Contamination of ether by water or alcohol changes its boiling point and specific gravity [0.725–0.728 U.S.P.] and can consequently be readily recognized. Among other tests for purity prescribed by the pharmacopœia are, that it should not color litmus paper nor be colored within an hour with a solution of potassium hydrate. Ether which is to be used for anæsthesia should be shielded from light and should be kept in tightly stoppered containers, as it is itself very inflammable and, as a mixture of ether and air explodes with great violence, ether narcosis should not be conducted in the presence of unprotected flames.

Local Irritant Action.—Ether vapor, being very volatile, has a high vapor tension, even when it is dissolved in the body fluids, and consequently it penetrates the tissues with extreme ease, irritating, at the point of application, susceptible tissue elements, particularly the nerve-fibres and the vessel walls. When ether thus penetrates the tissues, the sensory nerve-endings are first intensely irritated for a short time, then their sensibility is depressed. These effects in the nerve-endings, combined with the cold produced by its evaporation, account for the local anæsthesia of the skin which may be produced by this drug, in which connection this action will be further discussed (p. 118).

The local irritation of the sensory nerve-endings also explains certain indirect effects on the central nervous system, for a certain portion of the effects produced by ether on the respiratory and circulatory centres is certainly due to reflexes caused by such sensory irritation.

The action of ether after absorption into the blood is almost exclusively exerted on the central nervous system, for, even when the paralysis of most of the functions of the central nervous system is well developed, the circulation is but little affected, ether behaving in this respect like alcohol. In general terms, the action of ether may be characterized as an *"alcohol action,"* which is concentrated in a short period of time and which is very pronounced. The chief difference is that, on account of the rapid absorption of ether, especially when it is inhaled, the earlier stages of the effects on the cerebrum are less prominent than is ordinarily the case in alcoholic intoxication. However, in the first stage of the action of ether, we find the same peculiar mixture of depression of some functions of the cerebrum and of motor excitation which has been described in the analysis of the action of alcohol. In the second stage of the action of ether, the anæsthesia is completely developed, just as is the case in very profound alcoholic intoxication, with depression of all the cerebral functions and also of the spinal reflex mechanisms, the centres in the

medulla being the last to be affected and the heart beating relatively well even when death results from cessation of the respiration.

Excretion.—Ether is excreted in the expired air, by far the largest portion leaving the body very rapidly.

As the effects of ether on the central nervous system in general agree with those of chloroform, these two drugs can well be considered and discussed together.

CHLOROFORM, trichlormethane, $CHCl_3$, is a clear, colorless fluid, boiling at 62° C., the vapor having a sweetish odor and taste. It is very slightly soluble in water (about 1:200), but miscible with alcohol, ether, and the fatty oils in any proportion. In contradistinction to that of ether, chloroform vapor is neither inflammable nor explosive. However, the anæsthetization with chloroform in the presence of gas-lights is attended with certain disadvantages, as, in the combustion of its vapor, the gas, phosgen, CCl_2O, and hydrochloric acid are formed, both of which are very irritant to the mucous membranes (*Gerlinger*).

Properties.—As chloroform decomposes readily under the influence of light and air, it should be kept in opaque and completely filled containers. As the addition of a small amount of alcohol renders it more stable, the pharmacopœia permits it to contain 0.6–1 per cent. of alcohol.

Liebig and *Soubeyran* prepared chloroform for the first time at about the same time,—the former by allowing KOH to act upon chloral, and the latter by distilling alcohol with chlorinated lime; the latter method of preparation being the one which is more generally used. If impure alcohol is used in its manufacture, an impure product is obtained which must be purified. A completely pure chloroform may be obtained from chloral by decomposing it with soda, while other pure forms may be obtained by distilling acetone with chlorinated lime or by crystallizing chloroform by cooling to —70 to —80° C., or from its crystalline compound with salicylic acid anhydride. However, these absolutely pure chloroforms possess no advantages for medicinal purposes over the chloroform of the pharmacopœia, which has a specific gravity of 1.490.

The Pharmacopœial tests for the detection of impurities are reliable and give a guaranty of its purity quite sufficient for its employment by physicians. [If some chloroform be allowed to evaporate in a watch-glass, the last drop should have an irritant effect when inhaled. Distilled water shaken up with chloroform should give no reaction with potassium iodide and starch, nor with silver nitrate, nor should such water redden litmus paper. When left in contact with concentrated sulphuric acid, chloroform should not be darkened in color in less than one hour.—TR.]

Local Irritant Action.—In equal concentration chloroform is far more irritant to the tissues than is ether. When applied to the external skin, it causes first a feeling of coolness due to evaporation, then burning and reddening. If its evaporation is prevented, it may cause active inflammation and the formation of blisters. Dissolved in oil it produces a less intense but more lasting irritation of the skin. Its local irritant effects are even more pronounced on the mucous membranes, so that, when poisoning has resulted from swallowing chloroform, serious lesions of the stomach and bloody vomiting and diarrhœa result.

Excretion.—Much the larger portion of the chloroform is excreted through the lungs and with great rapidity, but a small portion is

decomposed in the body, and as a result the chlorides in the urine are increased (*Zeller*).

The narcotic action of chloroform, as also that of ether, is a very general one. Wherever in the organic world sensory and motor phenomena are to be found, these expressions of life are abolished if these anæsthetics are applied in sufficient concentration. The alterations in cell functions caused by them may be best observed if motor phenomena occur as a visible expression of cell life. In plants they abolish the movement of the protoplasm. The experiments on the sensitive plant, Mimosa pudica, the irritability of which is, for the time being, abolished by the action of anæsthetics, is a striking demonstration of such action (*Dutrochet, Leclerc, P. Bert*) (for further literature on the action of narcotics on plants see *O. Richter*). Their influence on motor phenomena in animal cells may be very simply demonstrated on ciliated epithelium, the ciliary movements of the epithelium in the mucous membrane of the posterior portion of the frog's throat being no longer able to move a small particle placed on its surface if it be exposed to an anæsthetic gas.

With a more pronounced degree of toxic action, death ensues in the cells of all tissues, the red blood-cells are destroyed by stronger concentrations, and rigor of the muscles ensues (*Kussmaul*) and the peripheral nerves are rendered unexcitable (*I. Bernstein*). However, all such effects, which may be produced by anæsthetics on the blood, the muscles, and the peripheral nerves outside of the body, are of no significance in connection with the use of the anæsthetics in medicine, for the central nervous system and also the heart are so much more susceptible that death occurs as a result of paralysis of the respiration and the heart long before these cells are affected. [Some destruction of the red cells does, however, occur during ordinary anæsthesia, particularly if this be prolonged or is very deep.—Tr.]. *It is owing to this much greater susceptibility of the nervous system that anæsthetics, which are fundamentally toxic to all living cells, may be employed to influence solely the functions of perception and action. They may be used as anæsthetics primarily because they depress first the cerebrum and then the spinal reflex centres, while the respiratory centre resists their paralytic action longer than all other portions of the central nervous system.*

Clinical Picture of General Anæsthesia.—At the commencement of the anæsthesia a condition resembling intoxication develops, during which the consciousness is clouded and is occupied by confused ideas. At this time there is more or less well-developed motor restlessness, and consequently this is often spoken of as the stage of excitement. Loud and foolish talking, laughing, etc., and active movements may occur, the face being reddened and the pupils dilated. While these symptoms of excitement are in many cases, particularly in women and children, but little developed and pass off rapidly, in

men, and especially in potators, they may be so marked as to resemble delirium of maniacal attacks. The more rapidly the concentration of the anæsthetic in the blood increases, the more rapidly does this stage pass over into that of complete unconsciousness. When this develops, the eyes assume the same position as in normal sleep, being turned inward and upward and the pupils being somewhat contracted. The sensibility is already abolished, although the reflexes still exist at this stage, and, in fact, even earlier, at a time when the sense of touch is but slightly impaired and when the patient may still be awakened by shouting and shaking, analgesia is already present. *This analgesia, developing before complete abolition of the consciousness, may be utilized for the performance of many minor operations.*

Some time after the complete abolition of the cerebral functions the reflex centres in the cord become paralyzed, and with the disappearance of the reflexes the muscle tone is also abolished, so that the anæsthetized patient lies completely relaxed, motionless, and without sensation. A stage, named by some the stage of toleration, by others the stage of surgical anæsthesia, has now been reached. Among the reflexes the last to disappear is the corneal reflex, whose disappearance, as is well known, is the signal for the surgeon that the further administration of the anæsthetic should be limited. Even in complete anæsthesia the pupils should remain contracted, their gradual dilatation indicating an insufficient respiration, while their sudden dilatation is a sign of imminent danger to life. [As the pupils also dilate during recovery from the anæsthetic, their dilatation may also be an indication of this.—Tr.]

As a rule, in chloroform anæsthesia the pulse is but slightly slowed, and after a time the face becomes pale. Marked retardation of the pulse to 50 beats or less per minute and extreme pallor are signs of a dangerous impairment of the circulation. In ether anæsthesia, on the contrary, the face remains flushed and the pulse is usually somewhat accelerated. [If before operation the pulse has been abnormally rapid, it very frequently is distinctly slowed and strengthened.—Tr.] In complete anæsthesia with ether or chloroform the respiration should be somewhat slowed, but should be regular and sufficiently deep.

Influence on Motor and Sensory Functions.—The mere surface picture of anæsthesia shows that the sensibility of the cerebral cortex is abolished before the motor functions, perception of pain and touch being abolished at a stage in which the consciousness is still filled with dreams which cause active movements. The observations of *Hitzig* have clearly demonstrated this difference in the susceptibility of the sensory and motor functions of the cortex.

During his experiments in stimulation of the cerebral cortex, this author found that the irritability of the motor portion of the cortex was abolished only during very deep ether narcosis. "Even when every trace of reflexes

had disappeared, when even the most intense sensory stimuli, such as those caused by pulling on the dura or by strong induction currents in the nasal mucous membrane, no longer produced any reflex effects whatever, some of the motor centres still reacted to local stimulation." For the pharmacologist it is an interesting fact that while ether is finally able to prevent any effects from stimulation of the cerebral cortex, *Hitzig* found that morphine never weakened the effects of such stimulation, even when very large doses were administered intravenously. This clearly demonstrates the fundamental difference between the action of chloroform and ether and that of morphine on the motor tracts.

Bernstein has shown that the spinal cord of the frog behaves in the same fashion as the cerebral cortex. This author, by stoppage of the blood flow through the lower portion of the spinal cord, protected this portion of the cord from the action of chloroform present in the blood, and found that the motor organs in the poisoned portion of the cord were, under these conditions, able to react to stimuli reaching them from the lower unpoisoned portion although the sensory receptive organs in the upper poisoned portion were already completely inexcitable.

It therefore appears that everywhere in the central nervous system the motor organs become narcotized much later than the sensory ones. It is significant, in this connection, that the respiratory centres, which maintain the respiratory movements long after any reactions to sensory stimuli have ceased to occur, are automatic motor centres.

Many facts indicate further that the motor centres experience an augmentation of their excitability before they are depressed by these anæsthetics. *Kräpelin,* in psychophysical experiments, was able to demonstrate a facilitation of the inauguration of motor acts during the earlier phases of the alteration of the consciousness produced by ether and chloroform, while, on the other hand, perception was retarded from the start. It therefore appears that these two phases of mental activity, the perception of external impressions and the motor innervation, are influenced in opposite fashions, just as is the case during the earlier stages of the action of alcohol.

This close relationship in the psychical effects of alcohol and of small doses of ether is also expressed by the fact that ether too produces a distinct euphoria, which fact accounts for the occasional occurrence of the chronic abuse of ether (*Ewald*). It is stated that in Ireland ether drinking is a comparatively wide-spread vice.

The excitability of the peripheral nerve-trunks is certainly at first markedly augmented by the local action of chloroform or ether, this effect being followed by a depression and finally by the abolition of their excitability if they are further exposed to the action of these vapors (*Bernstein, Waller* and *Bethe*).

The primarily stimulating effect of ether and chloroform, like that of alcohol, occurs also in vegetable cells, *Elfving* having found the respiration of plants to be increased by these drugs, while, according to *Kegel,* they also increase the assimilation of CO_2.

While the narcotic actions of ether and chloroform on the cerebrum differ from each other only quantitatively, when, disregarding their anæsthetic actions, we investigate the disturbances and alterations of

function which occur during anæsthesia, we find very essential differences in the actions of these two most widely used anæsthetics.

CERTAIN DISTURBANCES OCCURRING DURING ANÆSTHESIA are merely mechanical results of the muscular relaxation,—for example, the interference with respiration and asphyxia, occasioned by the tongue falling back on the larynx, and the interference with the power of swallowing, which may cause aspiration pneumonia. Another frequent disturbance, particularly at the start, is vomiting, which is probably of central causation, and not due to the local irritating effects of the anæsthetic which may be swallowed with the saliva. [The local irritating effect in the pharynx doubtless at times plays a rôle in producing such vomiting, and it also seems to the translator that the local irritating effects, especially of ether, in the stomach, which frequently appear to cause a free secretion of hydrochloric acid, cannot be disregarded as a probable contributory cause of the nausea and vomiting which follow the recovery from the anæsthetic.—TR.]

Annoying Reflexes.—When the vapor of ether or chloroform is inhaled, there occur a number of reflexes, just as is the case after the inhalation of other irritating gases, which reactions may be considered to be, as it were, defensive in their nature, by the aid of which the organism endeavors to guard the respiratory tract from the entrance of irritating vapors. Especially in experiments on animals there occurs with great regularity a stoppage of the respiration in the phase of expiration, or violent expiratory efforts and convulsive closure of the pharynx, which are due to reflexes originating in the nasal mucous membrane as a result of the irritation of the terminations of the trigeminus (*Kratschner*). The more concentrated the vapors inhaled, the more well developed is this reflex. After a short period, this stoppage of the respiration passes off, and the breathing then continues regularly and deeply (see Fig. 4). Simultaneously with this inhibition of the respiration, there often occurs a very pronounced slowing of the pulse, which also is reflexly induced, and at times the heart may cease to beat temporarily. [This reflex inhibition of the heart would appear to be a contributory cause of death in some cases of sudden death at the very commencement of chloroform anæsthesia.—TR.]

In man these reflexes produce slighter effects than in the rabbit or in the cat, and consequently, if one commences the anæsthetization very gradually, administering such slight concentrations of the anæsthetic that they produce only slight irritation, and if this concentration be only gradually increased, as a rule these disturbing reflexes may be completely avoided, for the reflex centres will be sufficiently narcotized to prevent their reaction to the irritation caused when the concentration of the inhaled anæsthetic is great enough to produce its local irritating effect in the upper air-passages.

The first EFFECTS ON THE RESPIRATION produced by the anæsthetic

after its absorption are an acceleration and deepening of the respiratory movements, which may be best observed in vagotomized subjects, for with intact vagi the reflex effects originating in the pulmonary nerves complicate the picture. *Knoll*[1] and *Cushny* go so far as to assume a primary excitation of the respiratory centre. In the stage of surgical anæsthesia the breathing, which during the stage of excitement was irregular, becomes regular and slightly slowed, and, as the sensibility is abolished, the respiratory centre is no longer affected by any reflexes, even long before it is itself depressed (*Cushny*). If the narcosis is pushed beyond the necessary stage, a final stage follows in which the breathing either gradually becomes shallower and shallower and finally stops entirely, or, but much less frequently, stops more or less suddenly. In general, observations on animals indicate that the *respiratory centre resists the action of full anæsthetizing doses of ether longer than it does those of chloroform,* and the practical experience of surgeons demonstrates that asphyxia occurs much less frequently with ether than with chloroform.

ACTION ON THE CIRCULATION

Vasomotor Centres.—There is a much greater difference between the two anæsthetics in respect to the intensity of their effects on the vasomotor centres and the heart. The vasomotor centres controlling the cutaneous vessels, and particularly those of the face, are, from the start, particularly depressed by ether and chloroform, and consequently at the start of the narcosis the face becomes flushed. When chloroform is inhaled, however, as a rule, the blood supply to the skin diminishes as the anæsthesia becomes deeper, because other vascular systems lose their tone and, as a consequence, the blood leaves the skin to go to these other regions. With ether, on the contrary, the face usually remains flushed, for the vasomotor centres controlling other vascular systems are much less affected by it than by chloroform.

Chloroform depresses the vasomotor centres far more than does ether, so that, even when chloroform anæsthesia is cautiously induced, the blood-pressure falls decidedly, while when ether is used it may for a long time remain at the normal level. In animal experiments this difference may be strikingly demonstrated if the animals are anæsthetized with doses of these two anæsthetics which are just sufficient to induce anæsthesia. While it is true that if the chloroform concentration of the blood is very gradually increased so that complete anæsthesia is induced only after 30–35 minutes of absolutely regular administration of the anæsthetic complete insensibility and complete abolition of the reflexes may be obtained without inducing any fall in the blood-pressure, with the continued maintenance of the same degree of anæsthesia the blood-pressure falls slowly and progressively, so that after about an hour it may be reduced to one-half of the normal height and after 2½ hours to one-third, while the respiration may

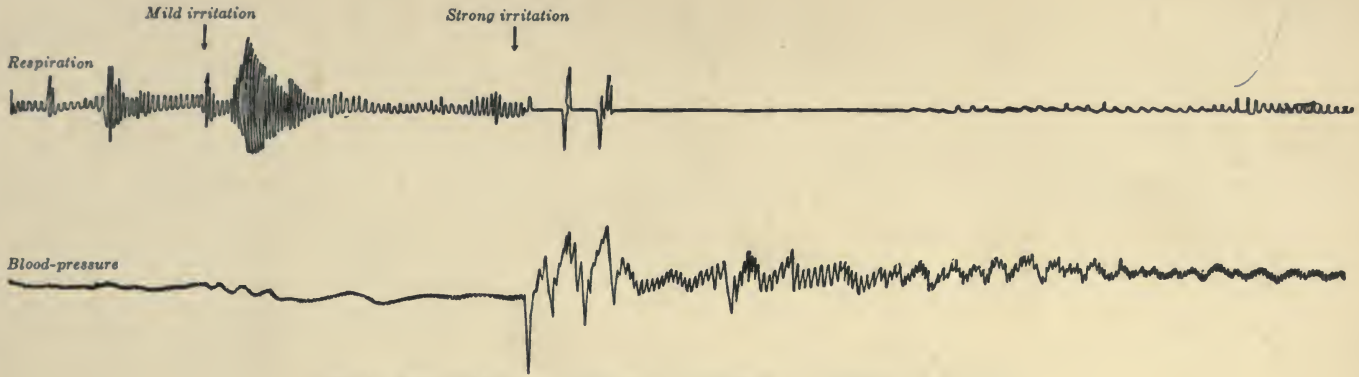

FIG. 4.—Forced inhalation of irritant gas. Reflex effects on respiration and circulation.

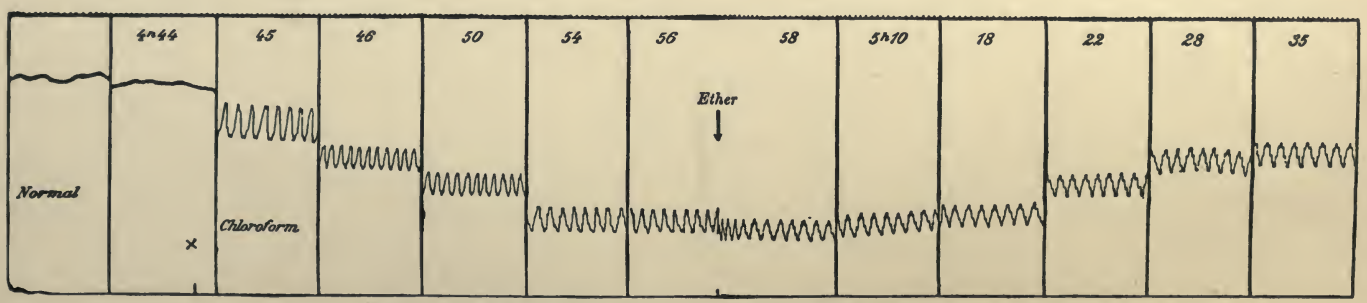

FIG. 5.—Comparative effects on blood-pressure of chloroform and ether.

continue regularly and normally (*Rosenfeld*). Such experiments indicate that the circulation is markedly impaired even by very cautiously conducted chloroform anæsthesia and relatively much more markedly than is the respiration. On the other hand, if ether be administered cautiously, complete anæsthesia is readily induced without causing any change in the blood-pressure, and even when the anæsthesia is continued for hours the carotid pressure need fall but slightly. In fact, if during a chloroform anæsthesia the blood-pressure has been caused to fall slowly and progressively and ether be substituted and the anæsthetization continued with it, the blood-pressure will gradually rise once more.

In man the same holds true. *Blauel*, using Gärtner's tonometer, found that in 100 ether anæsthesias of average duration the blood-pressure remained above the normal throughout, while in 37 chloroform anæsthesias it was regularly below the normal level.

Thus far the fall in blood-pressure during chloroform narcosis has been represented as the result of a depression of vasomotor centres, but without any presentation of proof that this is so. It is, however, clear that a gradual diminution in the power of the heart must also cause a fall in the blood-pressure, and earlier investigators have attributed this without question to a weakening of the cardiac action. *Scheinesson*[2] was the first to observe vasodilatation in the rabbit's ear during anæsthesia, which he attributed to depression of the vasomotor centres. In the rabbit, after section of the vasomotor nerves of one ear, the inhalation of chloroform causes a dilatation only of the vessels of the other ear whose nerves are still intact (*Knoll*[2]), and consequently it is evident that this vasodilatation is caused centrally. The acceleration of the blood flow from a mesenteric vein observed by *Pick* indicates that, when the vessels are relaxed during chloroform narcosis, the blood collects chiefly in the vessels of the lower abdomen. A similar depression of the vasomotor centres is caused by ether in a much slighter degree and only by much larger doses.

Action on the Heart.—It is very possible that in the usual chloroform narcosis, in addition to the vasomotor depression, a weakening of the heart action is also responsible for the gradual fall in blood-pressure, for, as will soon be discussed more fully, chloroform is a powerful cardiac poison in concentrations which are but slightly higher than that necessary for the induction of anæsthesia, and consequently even slighter concentrations may well produce such effects when acting on the heart for a considerable period. However, at the start the fall in blood-pressure is chiefly due to the depression of the vasomotor centres. This may be concluded from the fact that it is possible by very slowly increasing the amount of chloroform in the blood to cause complete paralysis of the vasomotor centres while the heart still continues to beat relatively well. Under such conditions the vasomotor centres are found to be completely insusceptible to stimulation by even

the most powerful stimuli, such as asphyxia or a sudden anæmia produced by ligating all the arteries passing to the brain, although at this time the moderately slowed but powerful heart-beats are still able to maintain the blood-pressure at a level corresponding to that observed after the complete relaxation of the vessels which follows section of the cervical cord.

The greater the concentration of the chloroform in the blood, the more evident does its action on the heart become. As a consequence, irregularities in the heart-beat may often be noted early in a chloroform anæsthesia, for the percentage of chloroform in the blood necessary for the maintenance of a satisfactory anæsthesia—according to *Pohl* on an average 0.035 per cent.—is sufficient to weaken the heart's action, as shown by *Sherrington* and *Sowton* in their experiments on surviving mammalian hearts perfused with blood containing chloroform.

Moreover, without any direct participation of the heart, the results of the general vascular relaxation are dangerous enough, for, as the blood collects in the splanchnic vessels, the other portions of the body receive but little blood, the face of the anæsthetized subject becomes pale and his skin cold, while the pulse becomes weak, and collapse may occur during the anæsthesia.

Of greater practical importance than this gradual fall in the blood-pressure, occurring when chloroform is pushed too far, is the sudden cessation of the cardiac activity, which may occur if *too large quantities reach the blood at one time.* With ether this danger is far less imminent, for the difference in the concentration of the drug which is sufficient for anæsthesia and that which causes cessation of the heart's activity is much smaller with chloroform than with ether. This is, from the practical point of view, the decisive difference between these two anæsthetics.

Chloroform a Cardiac Poison.—The earlier investigators also noticed that chloroform impaired the activity of the heart, *Snow,* as early as 1852, having observed that the vapor of chloroform when directly applied to the exposed heart stopped its beating. Later, *Scheinesson*[1] demonstrated that the cardiac activity was impaired by the inhalation of chloroform, and numerous later experiments in which various methods were employed have brought further proof that this is so.*

Newer experimental methods have rendered it possible to demonstrate in the most complete fashion the harmful effect of chloroform on the isolated mammalian heart. While these methods will be more

* Among others, mention should be made of the interesting experiments of *Gaskell* and *Shore* in which, with the aid of a cross-circulation between two animals, the blood containing chloroform acted in one only on the central nervous system, while in the other it acted only on the heart. In these experiments the blood-pressure always fell when the blood containing the chloroform reached the heart.

fully discussed in the chapter on the Pharmacology of the Circulation, their results are briefly given here. *Bock,* making use of an experimental method in which the blood-pressure depends exclusively on the work done by the heart, has shown that the inhalation of chloroform mixed with air is immediately followed by a fall in the blood-pressure and that the heart-beats are slowed independently of any action on the central nervous system, while the inhalation of strong ether vapor, even when continued for a considerable period, alters the blood-pressure and frequency of the heart-beats but slightly.

By experiments on artificially perfused hearts it has been possible to determine quantitatively the great difference in the action exerted on the heart by these two anæsthetics. Those conducted by *Dieballa* on frogs' hearts, and numerous more recent experiments conducted on surviving mammalian hearts, have demonstrated that the molecular concentrations of chloroform and ether which produce death of the heart are in the proportion of 1 to 30–35. *Pohl* found 0.058 per cent. of chloroform in the blood contained in the left ventricle of a dog which had been narcotized until the heart stopped.* As, according to this author, the concentration of chloroform in the blood when the narcosis is deep, but while the heart is still beating well, is on the average 0.035 per cent., and according to *Nicloux* 0.05 per cent., these figures show conclusively how slight the difference is between the concentration necessary for the maintenance of anæsthesia and that which causes paralysis of the heart. Here we find the explanation of the cases of sudden heart death which occur during chloroform anæsthesia. With ether such cases do not occur.

Cardiac Death in Chloroform Narcosis.—In order clearly to understand the danger to which the heart is exposed by the administration of concentrated chloroform vapor, one must remember that with incautious dosage the heart is the first organ to be imperilled. In a sense we are dealing with a local action of the chloroform-laden blood on this organ, for the blood which contains the largest amount of the anæsthetic flows directly into the heart, and only later is the anæsthetic distributed around in all portions of the circulation. The heart can therefore be very seriously poisoned by the sudden entrance into it of blood containing too much chloroform, even before any general narcosis has developed. If by such abrupt administration of chloroform the action of the left ventricle is markedly weakened for even a short time, a vicious circle is produced, which with each instant augments the damage suffered by the heart, for, as the heart empties itself but incompletely, it is directly exposed to a persisting

* In one case in which *Pohl* had forced air saturated with chloroform into the lungs and in which immediate heart death occurred, as much as 0.22 per cent. was found in the blood contained in the heart. However, in this case it is highly probable that a great excess of chloroform entered the blood during the last respiration.

poisonous action of the blood stagnating in it and containing poisonous amounts of chloroform, and consequently the continuation of this condition results in death of the heart. This is the reason why, when the heart is suddenly paralyzed by too large doses of chloroform, it is no longer possible to revive it by ceasing the administration of the drug and inaugurating artificial respiration. Under such conditions it may be revived only if this blood, which is saturated with chloroform, be removed from the heart, which may be accomplished by compression of the thorax, and in case of need by the intravenous (or intracardiac) administration of epinephrin 1 to 100,000 (see chapter on Circulation) [or by transdiaphragmatic massage of the heart, which has already under such conditions been the means of saving a considerable number of lives.—Tr.]

As is to be expected from the manner in which it occurs, chloroform heart death presents a materially different appearance from that of death due to vasomotor paralysis. This may be readily demonstrated in the laboratory by compelling an animal to inhale all at once large quantities of chloroform, in which case the blood-pressure falls more or less suddenly and the cardiac pulsations disappear completely. After cessation of the circulation, however, several respiratory movements occur, and in fact convulsions due to asphyxia may occur just as in any other sudden stoppage of the circulation. In this case the stoppage of the heart puts an end to life before deep narcosis has been attained. (See Fig. 6.)

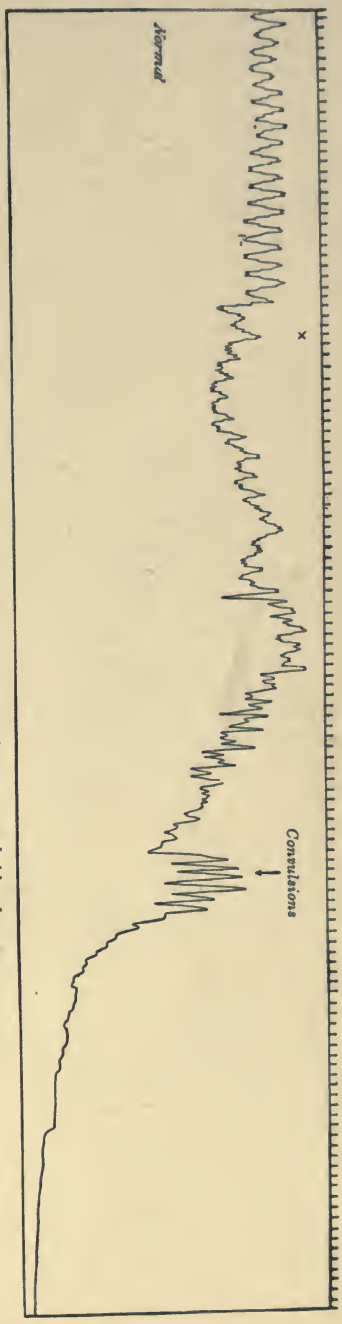

Fig. 6.—Sudden heart death from administration of concentrated chloroform vapor.

Many cases cited in the literature, in which death has occurred after a few inhalations of chloroform, were certainly due to such sudden overloading of the blood with chloroform as a result of careless pouring on the mask of too large amounts of the anæsthetic. The comment often made in such cases, that death could not have been due to administration of too much chloroform because not enough had been given to produce narcosis, is only explainable by the fact that the observer had thoroughly misunderstood the true cause of death.

Analysis of the Causes of Experimental Chloroform Death.—In considering the evidence which has been furnished by animal experimentation, in regard to the causes of death by chloroform, it is seen that two forms may be distinguished. With the gradual absorption of too large quantities of chloroform, all the organs succumb to the poison in fairly equal degree, and the abolition of the functions of the different portions of the central nervous system occurs in the order of their relative susceptibility. As the vasomotor centre suffers very early, a stair-like fall in the blood-pressure results from the general vascular paresis, and finally the respiration fails, death resulting from the cessation of the breathing, although the heart continues to beat regularly and with a fair degree of force. The heart is consequently the last to die in this form, which resembles the usual death occurring in ether narcosis. In the other form, large amounts of chloroform pass rapidly into the blood and paralysis of the heart results, and, as the poisoned heart is unable to expel this blood, which is saturated with large amounts of chloroform, from its cavities and vessels, actual death of the heart quickly follows the paralysis. In this form of chloroform death, the respiration continues after the heart has ceased to beat.

As in practice intermediate forms between, and combination forms of, these two occur, the consequent varying course and appearance of fatal chloroform accidents have led to an active discussion as to whether death in chloroform narcosis is due to respiratory or cardiac paralysis. Particularly the Paris Commission of 1855, the English Commission of 1864, and the two Indian Commissions of 1889 and of 1890, have, by means of numerous experiments on different species of animals, firmly established the fact that a proper administration of not too concentrated chloroform vapor, if persisted in, always results in the respiration stopping first, while the heart continues to beat for some time—2 to 12 minutes—longer. On the other hand, other authors have repeatedly emphasized the fact that death may also result from a primary stoppage of the heart (*Scheinesson*,[1],[2] *Schmey*, *Cushny*, *Ratimoff*, and others). From what has been said above, these contradictions in the experimental results are readily explained by the variations in the experimental conditions.

Chloroform Death in Man.—Actual experience with chloroform death in man agrees with the experimental data, except that in man one often is dealing with individuals whose hearts have already been weakened by degenerative changes. Among the autopsy findings after sudden death from chloroform, very frequently fatty degeneration

of the heart is noted. Consequently it is easy to understand why in man death due to the heart should occur with relatively greater frequency than is the case in experiments on animals.

If the chloroform accumulates in gradually increasing amounts in the blood, extreme pallor of the face and cyanosis develop, as expressions of the fact that the vasomotor and respiratory centres have become incapable of performing their functions, and asphyxia occurs while the heart continues to beat. If in such cases artificial respiration be instituted promptly enough, the natural respiratory movements, as a rule, start up again as soon as the excess of chloroform has been eliminated. However, cases do occur in which the respiration does not return although the heart clearly continues to beat for some time longer.

Nothnagel and *Rossbach* mention such a case in which artificial respiration was carried on in a most efficient fashion for half an hour, as long as the heart continued to beat, without any reappearance of the voluntary respirations. Quite characteristic of such irreparable respiratory paralysis in the presence of a heart which continued to beat well, is the description of *Jenop's* case of a man, aged 48, to whom chloroform was to be administered on account of the amputation of a finger. "The patient was more restless than usual and was completely anæsthetized after the administration of not more than two drachms of chloroform. The operation was about to start, when he snorted two or three times, suddenly became blue in the face and ceased breathing, while the radial pulse became very weak. The heart sounds were audible for 20 minutes longer, during which time no visible respiratory movements occurred." All attempts at revival were unsuccessful. Post-mortem examination disclosed nothing of any particular moment.

If the face of the chloroform patient suddenly becomes pale, the pupils dilate and become fixed, the pulse disappears, and the heart ceases to beat, while the respiration continues for some time, the prospects for revival are much less favorable. This is the picture seen in heart death due to sudden overloading of the pulmonary blood with chloroform. Such accidents occur usually at the commencement of the anæsthesia, when the patient is violently excited and the anæsthetist attempts to attain surgical anæsthesia too rapidly, or, with an excited patient, endeavors to control him by incautiously pouring too much chloroform on the mask. From many typical reports of such cases, the following may be cited from *Schmey:*

For the purpose of removing a gland from the submaxillary region in a man of 45 years, anæsthesia was started. "At the very start, however, when only a few cubic centimetres of chloroform had been poured on the mask, the patient suddenly became pulseless, but continued to breathe quietly and deeply several times more. Artificial respiration was instituted, and a pulsation in the radial artery could be clearly felt each time pressure was made on the thorax. If then the artificial respiration was stopped, natural breathing was continued for a short time, but no spontaneous pulse in the radial artery could be felt. Artificial respiration was instituted again with the same effect, and this was continued for longer than an hour with similar results." The autopsy disclosed marked fatty degeneration of the heart.

In many cases of death occurring at the start of the anæsthesia, *death has been attributed to the effects of shock,* and cases certainly

vouched for (*Nussbaum*) do in fact demonstrate that, under similar circumstances of marked excitement in especially feeble persons, cardiac death may result from varying sensory stimuli without any anæsthetic whatever having been administered. It is not inconceivable, consequently, that the first inhalations of the irritating vapors of chloroform or ether may cause death through their reflex effects on the respiration and the heart without there being any question of an overdose having been administered. However, these reflex effects which have been mentioned before, the stoppage of the respiration in expiration and the inhibitory stoppage of the heart, are much less pronounced in man than in animals and pass off rapidly. It is very improbable that they play any important rôle in the accidents of anæsthesia, especially as these reflex effects are by no means slighter when ether is inhaled than when chloroform is administered, and yet such accidents occur more frequently with the latter anæsthetic. In any case, especially if the narcosis be gradually induced, the reflex inhibition of the heart may be certainly prevented by previously administering atropine (½ mg.) and the marked reflex effects on the respiration by that of morphine (0.01–0.2 ! gm.).

Avoidability of Anæsthetic Accidents.—The foregoing discussion of the dangers to the respiration and circulation which attend anæsthesia shows clearly that the boundary between sleep and death in deep narcosis is small enough. However, at the same time our knowledge of the causes of these dangers makes it equally clear that, *in the great majority of cases, these accidents may be avoided, for they are practically always the results of a faulty management and incautious dosage of the anæsthetic.*

The anæsthetic methods of the day are very susceptible of an improvement which would permit of an exact and reliable means of varying and controlling the degree of narcosis produced. However, even with the methods usually employed at the present time, it is possible to avoid these dangers if the anæsthetist understands the conditions controlling the absorption and elimination of the anæsthetic and is thus in a position to appreciate correctly the causes of these possible dangers.

Laws Governing the Absorption and Distribution of Anæsthetic Gases.—The absorption of chloroform or ether vapors by the blood depends on the plasma's coefficient of absorption for these gases and on the temperature and the partial pressure of the anæsthetic in the alveolar air. As the absorption coefficient at body temperature may be considered as constant, the absorption of chloroform or ether at any instant is directly proportional to the partial pressure of the anæsthetic in the inspired air,—*i.e.*, to its volume per cent.

It goes without saying that the more the functional nervous elements are permeated by the anæsthetic the more pronounced will be its action on the nervous system. The distribution of chloroform or ether throughout the organism follows certain well-defined laws, the

cells of all tissues, and especially those of the nervous system, having a greater affinity for them than has the plasma. The cause of this unequal partition of the anæsthetic between the nutrient fluid and the cellular elements has been found, as will be more fully discussed later, to lie in the greater power to dissolve chloroform with which the cells are endowed on account of the presence in them of fat-like or lipoid substances such as cholesterin, lecithin, etc. According as the cells in different regions contain larger or smaller amounts of such lipoids, they absorb larger or smaller quantities of chloroform. In consequence, therefore, of their greater power of dissolving the anæsthetic, the tissues absorb it in greater concentration from the blood, and consequently, at the commencement of every narcosis, the blood returns to the right heart from the systemic circulation containing less chloroform than is carried to the tissues from the left heart. According to *Nicloux's* analyses, venous blood of dogs, even when full anæsthesia has been maintained for a considerable period, contains on an average 0.05 per cent. of chloroform while the arterial blood contains 0.06–0.07 per cent. At the commencement of anæsthetization this difference is naturally much greater, and consequently when the anæsthetic is administered incautiously the left heart is much more exposed to danger than is the right. For example, *Pohl* found 0.22 per cent. of chloroform in the blood of the left ventricle but only 0.02 per cent. on the right side in a dog in which he had brought about a sudden cardiac death by the rapid administration of air saturated with chloroform. Such are the conditions in those cases in which the overloading of the blood in the lungs with chloroform may poison the left heart before the chloroform is sufficiently distributed and absorbed by the other tissues and consequently before any narcosis develops. On the other hand, when a properly induced anæsthesia is at its height, the central nervous system contains relatively more chloroform than does the blood.

However, the tissues are never able to remove all the chloroform from the blood. On the contrary, with continuous inhalation a condition of equilibrium between blood and tissue cells must gradually be established, which corresponds to the distribution coefficient of the solubility of the chloroform in the blood fluid and in the body tissues. When, on the other hand, further administration ceases and the elimination through the lungs commences, so that the concentration in the blood diminishes, it necessarily follows that the chloroform moves in the reverse direction, from the tissues back into the blood. Naturally, with persisting elimination the normal functions are again established.

These phenomena may be compared with extraction by agitation when a substance less soluble in water than in another fluid, used as an extractor, distributes itself between the two fluids and, in accordance with its greater solubility in the second fluid, accumulates in larger quantities therein, and yet may be removed from this fluid again if repeatedly extracted with pure water. In the body, chloroform at

each moment distributes itself between the blood and tissues in accordance with its relative solubility therein, just as occurs in the method of extraction by shaking.

The amount of chloroform present in the central nervous system is consequently always proportional to the amount present in the blood supplying this organ. Step by step it follows the chloroform partial pressure as it rises or falls in the blood. The *amount of chloroform present in the blood* is, however, for its part also *dependent* in an entirely similar fashion *on the chloroform partial pressure in the inspired* air,—*i.e.*, on the volume per cent. of its vapor in the alveoli. *The depth of narcosis consequently is increased or diminished in direct proportion to the concentration of the anæsthetic in the air inspired.*

The various events and happenings in anæsthesia thus occur in the following fashion.

In the lungs there occurs an exchange between the blood and the inspired air in which, with a given concentration of chloroform in the air, the blood absorbs from it a certain portion, and consequently at the start less of the anæsthetic is contained in the expired than in the inspired air. For example, *Harcourt* found 0.55 per cent. $CHCl_3$ in the inspired air but only 0.34 per cent. in that expired at this time, this showing that the blood had given up a considerable portion of its chloroform to the tissues. This continues until a condition of equilibrium has been established between the chloroform content of the blood and that of the tissues. In the meantime, so long as the blood returns to the lungs from the tissues poorer in chloroform than when it left them, it must compensate for this loss by absorbing chloroform from the alveolar air until the chloroform tension of the blood and the alveolar air is equalized. With the inhalation of a mixture with constant chloroform content, there is a constant flow of chloroform from the inspired air to the blood and from this to the tissue cells until the chloroform tension of the tissues and of the blood has become equal to that of the air inspired. When this state has been attained, the percentage of chloroform in the blood and in the tissues remains unchanged as long as the amount of the chloroform in the air respired remains constant. If the chloroform content of the air breathed be increased, the same play as formerly repeats itself, more chloroform being taken up by the blood and consequently more being absorbed by the tissues from the blood until the partial pressure of chloroform in the tissues, in the blood, and in the alveolar air has again become equal.*

If the administration of chloroform ceases entirely, the blood at the start gets rid of the chloroform very rapidly, and, corresponding

* Recent analyses by *Nicloux* give 0.05 per cent. of chloroform and 0.13–0.14 per cent. of ether as average figures for the amounts of these substances present in the blood during deep anæsthesia.

to its lessened tension in the blood, chloroform rapidly passes from the tissues into the blood and thus starts a current in the opposite direction,—*i.e.*, from the tissues through the blood to the expired air. If the air inspired contains no chloroform, the chloroform contained in the nervous system after a short time becomes so diminished that it is no longer sufficient to maintain narcosis, and the patient wakes up. The last portions of the chloroform, however, are relatively slowly eliminated, for the tissues possess a much stronger affinity for the drug than that of water. This gradual diminution of the chloroform present in the blood of anæsthetized dogs is illustrated in the following table of *Nicloux*, in which it may be seen that chloroform may be recognized in the blood even seven hours after discontinuation of its administration.

Chloroform Content of Blood after Termination of Anæsthesia.

Time elapsed since termination of anæsthesia	Per cent. of chloroform in blood	
	Exp. 1	Exp. 2
0 minutes	0.054	0.0595
5 minutes	0.0255	.....
15 minutes	0.0205	.....
30 minutes	0.018	0.023
1 hour	0.0135	0.018
3 hours	.....	0.0075
7 hours	.....	0.0015

The elimination of ether from the blood takes place somewhat more rapidly, which explains the more rapid recovery from ether narcosis.

Ether Content of Blood after Termination of Anæsthesia.

Time elapsed since termination of anæsthesia	Per cent. of ether in blood	
	Exp. 1	Exp. 2
0 minutes	0.115	0.159
3 minutes	0.071	0.108
5 minutes	0.063	0.080
15 minutes	0.052	0.058
1 hour	0.025	0.021
2 hours	.....	0.004

Laws Governing Dosage.—The symptoms in narcosis make it clear that *a certain degree of saturation of the tissues with the anæsthetic corresponds to every variation of the partial pressure of the gas in the alveolar air. The depth of the anæsthesia is consequently at every moment dependent on the partial pressure of the anæsthetic in the gas mixture respired.*

From this law, first propounded by the French physiologist *P. Bert,* follows the—for the management of anæsthesia—extremely important conclusion, that the depth of the narcosis and the danger thereof is not at all dependent on the absolute amount of the anæsthetic which has been used, but upon the concentration of the anæsthetic in the air respired. The control and modification of the degree of action, which with non-volatile drugs is attained by modification of the absolute size of the dose, is, during the administration of gases, attained by modification of the concentration administered. *Consequently in every moment of the anæsthesia a sufficient dilution of the anæsthetic with air is an essential condition.*

With *anæsthetics,* just as with non-volatile drugs, the *therapeutic and toxic doses must be determined.* With them it is necessary to establish the concentrations which produce a safe anæsthesia of sufficient depth, and one which may be maintained for some time without injury, and to find out at which concentrations the dangerous accidents may occur. The therapeutically efficient and toxic concentrations represent the limits for safe depth of anæsthesia. *Paul Bert* called this interval the "zone maniable."

Since the time of *Bert* many experiments, and in recent times with methods free from objections, have been undertaken in order to determine the *therapeutically effective* and the *toxic concentrations of chloroform and ether,* and the figures obtained agree closely enough for practical purposes. *Bert* [1,2] found 1.5 volume per cent. of chloroform vapor in the inspired air sufficient to produce narcosis, but this figure is too high, for *Kionka* [2] found that the concentration suitable to induce and maintain narcosis lies between 0.6 and 1.2 volumes per cent.

The following table gives the results of *Rosenfeld's* [1] experiments in which he investigated the intensity of the action produced in rabbits by different mixtures of air and chloroform:

Relationship between the Percentage of Chloroform and Ether in the Respired Air and the Depth of the Anæsthesia (Rosenfeld, Spenzer).

Chloroform, percentage by volume	Time necessary to induce anæsthesia	Depth of anæsthesia or narcosis	Remarks
0.54–0.69.....	2 hrs.....	No narcosis.....	Only somnolence.
0.96–1.01.....	30–40 min.....	Complete.....	Blood-pressure at first normal then gradual fall for 4 hrs. Respiration normal.
1.16–1.22.....	30 min.....	Complete.....	Cessation of respiration at end of 2 hrs.
1.41–1.47.....	37 min.....	Deep.....	As above after 1 hr.
1.63–1.65.....	12 min.....	Deep.....	As above after 30 min.

Relationship between the Percentage of Chloroform and Ether in the Respired Air and the Depth of the Anæsthesia (Rosenfeld, Spenzer)—Continued.

Ether, percentage by volume	Time necessary to induce anæsthesia	Depth of anæsthesia or narcosis	Remarks
1.5	2 hrs.	Hardly any	Only slight somnolence.
2.5		Very incomplete	Reflexes maintained.
3.2–3.6	25 min.	Complete	Respiration and cardiac function remained good for hours.
4.45	15 min.	Complete	Respiration slow and regular; pulse accelerated.
6.0			Respiration ceased in 8–10 minutes.

As may be seen from this table, for rabbits the efficient dose of ether lies between 3.5 and 6.0 per cent. by volume. In man similar concentrations are sufficient, as shown by *Dreser,*[1] who, at the height of deep ether narcosis, collected air from under the mask and found in it on the average 3.7 per cent. by volume.

It is thus seen that a concentration of about 1 per cent. by volume of chloroform vapor is sufficient to maintain a complete anæsthesia in the rabbit, even for as long as four hours, with the respiration remaining normal and the blood-pressure falling only very slowly. However, anæsthesia is induced only very slowly with this low and consequently safe concentration. A concentration only slightly higher —for example, 1.6 per cent.—induces anæsthesia much more rapidly, but with this concentration the respiration may stop when its inhalation has been continued for half an hour. It is consequently clear that the *limit of safety is much smaller for chloroform than with ether, and this difference in the size of the difference between the therapeutic and the toxic concentration of the two anæsthetics is merely the exact expression and explanation of the now generally accepted clinical conclusion that chloroform narcosis is attended with a greater direct danger to life than is ether narcosis.* The comparison of the figures for the concentrations necessary for the induction of anæsthesia shows further that *with ether the percentage by volume present in the respired air must be at least three times larger than is the case with chloroform.*

After Dangers of Ether Narcosis.—In *ether narcosis* an *overdosage lasting for a short time is by no means so likely to produce direct disturbances of the circulation and respiration as is the case with chloroform.* On the other hand, if the permissible concentration be exceeded, *local irritant effects in the respiratory mucous membrane* result. A mixture of air with 7 per cent. of ether vapor is quite irritant to the mucous membrane of the larynx and causes a reflex

cough, and at times a temporary closure of the glottis, causing a feeling of suffocation (*Dreser*[2]). However, these reflexes, which act, as it were, as sentinels to prevent the entrance of irrespirable vapors into the lower air-passages, soon cease if the ether inhalation is continued, and the sensibility is thus further depressed. These irritant actions affect at the start the mucous membranes of the mouth, the naso-pharynx, and the upper air-passages. The salivary glands especially are stimulated to active secretion, and, as the anæsthetized individual can neither expectorate nor swallow, mucus and saliva collect in large amounts in the mouth and throat. Rattling respiration results, and *bronchitis* or *pneumonia* may develop some time later. It is questionable whether these inflammations are due to the direct irritation produced by the ether vapor in the tracheal and bronchial mucous membranes, or whether they result from the aspiration into the lungs of the saliva and mucus secreted so profusely (*Grossmann, Hölscher, Klipstein*). A hypodermic of atropine or scopolamine preceding the ether narcosis will entirely prevent or markedly lessen this hyper-secretion.

Chloroform anæsthesia also is followed by dangerous after effects if too high concentrations are administered, or even if the proper concentrations are administered for too long a time, *fatty degeneration of the liver, of the heart, and of the kidneys* developing under these conditions, all lesions which may be regularly demonstrated in animals after a single long-continued chloroformization of same (*Ungar, Strassmann, Ostertag*). They are due to a toxic action on the cells of these internal organs, which occurs along with the narcosis of the brain, but which is not dependent on the cerebral actions, for they may be caused by repeated subcutaneous injection of non-narcotic doses of chloroform, which produce similar lesions in the same organs (*Nothnagel*). The very intense fatty infiltration of the liver and of the heart, sometimes observed, is the expression of a very severe cell destruction (*Rosenfeld*[2] *u. Rubow*).

These experimental findings make clear the cause of those fatal cases in which, after chloroform anæsthesia, death occurs with the symptoms of serious liver disease or those of increasing cardiac weakness and coma (*Bandler, Ambrosius, Fränkel, Kast u. Mester*). The harmful after-effects on the kidney are evidenced by the frequent appearance of albumin and casts in the urine (*Rindskopf*). In addition, an increased destruction of proteid and the appearance in the urine of pathological decomposition products of proteids have been proved to occur (*Kast u. Mester*).

After ether all these metabolic disturbances are by no means so pronounced as after chloroform. In particular, *Selbach's* experiments have shown that even long-continued and frequently repeated ether narcoses do not so readily cause the death of animals as do repeated chloroform narcoses.

From what has been said it is evident that *almost all of the dangers*

of anæsthesia are due to the administration of too high concentrations of the anæsthetics. With chloroform even a slight overdosage directly imperils life, while the after-effects of ether on the respiratory organs are usually due to the inhalation for a considerable time of ether vapor which is insufficiently diluted with air.

Drop Method.—It follows that the drop method is the only one permissible for the administration of the more dangerous chloroform, for by this method the dosage may be physiologically varied,—*i.e.*, may, according to the observation of the symptoms of the anæsthetized patient, be administered drop by drop, at times more rapidly and at times more slowly, when once the necessary depth of anæsthesia has been attained.

In order to avoid the reflexes produced by too concentrated vapor, the administration should be started very gradually, at the rate of about 20 drops in the minute, this rate being gradually increased to, at the most, 60 drops in the minute, and, when surgical anæsthesia has been attained, the number of drops should again be diminished. On account of the lower boiling point of ether, it is much more difficult, when using the drop method and a loosely applied mask, to produce the concentration of the vapor which is needed for the induction of anæsthesia, and even with the use of closely applied masks it is not always possible to produce surgical anæsthesia by administering ether according to the drop method. Consequently, formerly ether was usually poured into the so-called half-closed masks, which were covered with impermeable material.

Surgical experience has shown that these methods permit of anæsthetization with a satisfactory degree of safety, but they possess the drawback that the rapidity with which the drops should follow each other from moment to moment is entirely dependent upon a subjective estimate by the anæsthetist, and that it is impossible under such conditions to estimate accurately how much of the anæsthetic actually gets into the air inspired under the momentary conditions. Many attempts have therefore been made to construct apparatus which with greater certainty may be adjusted for certain concentrations.

Anæsthetizing Apparatus.—The first attempts to conduct anæsthesia in man with such measured mixtures were made by *Paul Bert*.[3] *Dreser*[3] and *Geppert, Kionka*,[1,2] *Kermish*, and many others have constructed various apparatus by the use of which the uncertainties and accidents of anæsthesia should be eliminated. These exact apparatus are, however, too complicated for general use, and have therefore not been widely adopted. The *Roth-Dräger* apparatus is one of the most widely used, and in it the anæsthetic is administered diluted with oxygen. An absolute guarantee of the concentration of the anæsthetic in the respired air can be furnished only by such apparatus as lead an already measured mixture directly into the air-passages but not through a more or less closely applied mask. Such apparatus are used in animal experiments (*Kronecker, Ratimoff, Cushny*) but the same principle may be utilized for man.

Dependence of Absorption of the Type of Respiration.—If the anæsthetic be dropped on the mask or administered by means of apparatus through a mask which is not closely applied, the amount which is actually respired is markedly influenced by the rate and quality of the respirations. With each inspiration air from the outside rushes under and through the mask, and consequently rapid and deep

breathing on the part of the patient causes a dilution of the vapor under the mask, while the expirations force out a large portion of the anæsthetic which may be present in the mask, and thus, with active respiration, only a small portion of the anæsthetic used actually reaches the lungs. On the other hand, depression of the respiration necessarily to a high degree favors the accumulation of the anæsthetic inside the mask, and consequently, when for a considerable period the respiration is feeble, the air in the mask contains higher percentages of the anæsthetic.

Individual Susceptibility or Idiosyncrasy.—Consequently a painstaking observation of the respiration is essential, no matter what method is used in the anæsthetization, and, at the same time, all the other symptoms must be closely watched, for even in animals the susceptibility of different individuals of the same species to anæsthetics varies, and in man the susceptibility is subject to wide variations, just as is the case with alcohol. Consequently, as expressed by *v. Mikulicz,*[1] *every anæsthetization is a new experiment that must be continually controlled according to the reaction of the organism.*

Estimated by the average consumption of chloroform in the unit of time, women are generally more readily narcotized than men, and the resistance is greatest in middle life. It is well known with what difficulty chronic alcoholics are anæsthetized.

Comparative Mortality.—If the effects of chloroform be compared with those of ether, the facts already mentioned are alone sufficient to show that, when the permissible concentration is exceeded, the direct danger to life is very much greater in chloroform narcosis than in ether narcosis. The statistics of the Deutsche Gesellschaft für Chirurgie, 1903, place the mortality at one death in 3000 for chloroform, and only one in 14,600 for ether.*

Moreover, chloroform narcoses of rather long duration, even when carefully conducted, are accompanied by other dangers to the organism (p. 74), which cannot be avoided and which occur very rarely when ether is used. The hypersecretion which may cause serious after-effects when ether is used may, on the other hand, be avoided by the previous administration of atropine or scopolamine. Finally, the toxic action of chloroform on the heart forbids its use in patients with circulatory disease.

That, in spite of all this, chloroform is used so much is explained by the fact that complete anæsthesia is much more easily obtained with chloroform than with ether. For operations lasting but a short time the analgesia alone is sufficient, which is already present in the stage of excitement produced by ether, the so-called half-narcosis (*Sudeck, Mikulicz* [2]).

* [Recent American statistics give the mortality as one in 2048 for chloroform and one in 5623 for ether. (Gwathmey, J. of A.M.A., 1912, vol. lix, p. 1845).—Tr.]

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COMBINED ANÆSTHESIA

In order to avoid the chief disadvantages of ether, which are presented by the slow or difficult induction of insensibility and the usually very pronounced stage of excitement, the anæsthesia is often started with chloroform and then continued with ether. The use of ethyl bromide (*Kocher*) for this purpose has been properly abandoned.* It has also been possible to augment the anæsthetic effects of ether by combining it with other narcotics.

Soon after the introduction of general anæsthesia, on purely empirical grounds it was found advantageous to make use of mixtures of ether and chloroform, often with the addition of alcohol, in preference to using either of these anæsthetics alone. Apparently anæsthesia with such mixtures is less attended by the danger of depression of the heart and respiration than is pure chloroform anæsthesia.

In such mixtures the alcohol plays hardly any other rôle than that of diluent (*Filehne* and *Biberfeld*), for it is only the diminution of the vapor tension of the anæsthetics, caused by the addition of the alcohol, which can be of any significance, for, in its presence, the evaporation of the actually efficient constituents of the mixture is retarded, and thus the danger of overdosage is lessened.

With the combination of ether and chloroform, on the other hand, newer investigators of the reciprocal synergistic effect of the narcotics have raised the question whether the narcotic actions of ether and chloroform, when thus used, are simply superimposed on each other, or whether, as has also been assumed, they synergistically produce an increased effect. In the first case, half of the vapor concentration of ether necessary to produce anæsthesia and half of the similarly effective concentration of chloroform should be sufficient to produce anæsthesia, but should do no more than this. If, on the other hand, by their simultaneous action a synergistic increase in their action results, perhaps on account of a greater absorption of chloroform by the nervous tissues (*Fühner*), the total effect should be greater than would be expected from the simple addition of their separate effects.

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* [In the United States the less dangerous ethyl chloride is widely used as a means of easily, safely, and pleasantly starting the anæsthesia, and where it has been used has met with much favor.—Tr.]

Honigmann believes that he has been able, by experiments on animals, to show that this greater effect is produced, yet the average values obtained in his experiments do not indicate this, but only those obtained under special conditions. On the other hand, *Madelung*, by continuously administering exactly measured mixtures of ether and chloroform, was able to produce only that degree of anæsthesia which was to be expected as a result of a simple addition of the separate effects. In his experiments mixtures containing less than half the amount of chloroform necessary to produce anæsthesia failed to produce anæsthesia when combined with a concentration of ether equal to one-half of the anæsthetizing concentration. His results agree with those obtained by *Bürgi*, who was also unable to obtain any synergistic strengthening of the action of the hypnotics of the alcohol group, chloral hydrate and urethan, whose action is in principle the same as that of chloroform and ether. The advantage (? Tr.) of anæsthesia induced by such mixtures may consequently be attributed only to the fact that the dangerous actions of chloroform are exerted in the production of only one-half of the total narcotic effect.

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MORPHINE-SCOPOLAMINE ANÆSTHESIA

On the other hand, by combination with substances like *morphine* and *scopolamine*, which depress the central nervous system in a different manner, it is possible to produce a distinct augmentation of the narcotic effects of the gaseous anæsthetics. A preliminary injection of 0.01 gm. of morphine with 0.5 mg. of scopolamine not only prevents that stage of excitement which ordinarily is so disturbing at the commencement of anæsthesia, but in addition it renders it possible to induce and maintain a satisfactory anæsthesia with distinctly lower concentrations of the anæsthetic in the air inspired.

In experiments on animals it has been possible to confirm this clinical experience in an exact fashion, *Madelung*, after previous injection of doses of morphine and scopolamine, which by themselves produce no narcotic effects, having been able to induce a deep narcosis with air containing only 2.5–3 volume per cent. of ether, although the controls which had not received such injections required 4.5 per cent. of the anæsthetic for the induction of equally deep anæsthesia. Consequently, after the previous administration of these two drugs, human beings may be satisfactorily anæsthetized with minimal amounts of chloroform, or, in case ether be used, they may be readily anæsthetized by the safe drop method. In addition, scopolamine possesses the advantage, as has already been mentioned (p. 76), of inhibiting the secretion of saliva.

As stated by *Schneiderlin, Korff*, and many others, it is possible to produce with morphine and scopolamine alone a condition of analgesia and clouded consciousness (twilight sleep) in which even relatively major operations may be painlessly performed. It was such observations which first directed attention to the striking intensification of the effects of morphine which is caused by scopolamine and which may be readily demonstrated in experiments on animals (*Kochmann*).

Some time ago morphine-scopolamine narcosis was actually recommended as a substitute for the general anæsthesia induced by inhala-

tion; but further clinical experience, supported by the results of experiments on animals, has demonstrated that *those doses, which without the aid of one of the gaseous anæsthetics cause a narcosis of sufficient depth, carry with them greater dangers than any of the other various methods of producing anæsthesia* (*Kochmann*).

In principle, any narcosis produced by injecting a drug must represent a step backward when contrasted with anæsthesia produced by inhalation, for, when non-volatile narcotics are administered, one loses the greatest of advantages,—namely, the ability to interrupt the anæsthesia at the appearance of dangerous symptoms, and to secure the elimination of the drug in the most rapid manner possible by elimination through the lungs. Doses of morphine and scopolamine which, when given together, prepare the patient satisfactorily for an anæsthesia by inhalation are without danger. At the present time they are also often employed to produce a certain degree of cloudiness of the consciousness and loss of memory during parturition (*Gauss, Krönig, Mansfeld, Björkenheim*). When used for this latter indication, the morphine should be cautiously administered, in order to avoid the danger to the respiration of the new-born child, which has already been mentioned on page 35. While 0.3–0.6 to 1.0 mg. of scopolamine, administered in several injections, may be safely given, it is not well to increase the dose of morphine beyond 0.01 gm. in labor cases.

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NITROUS OXIDE ANÆSTHESIA

The great majority of accidents during chloroform and ether narcoses occur during minor operations, for which one attempts to induce an anæsthesia of short duration too rapidly and without sufficient assistance. The introduction of nitrous oxide, as a means of rapidly producing a narcosis of short duration, was consequently an important step of progress, although to-day local anæsthesia has almost entirely driven this method out of the field for minor surgical procedures.

Nitrous oxide, N_2O, whose powers of causing intoxication are responsible for the discovery of inhalation anæsthesia, was actually introduced into practice only at a much later date, the sixth decade of the last century.

This substance is a colorless gas with a weak, sweetish odor, heavier than air, and rather soluble in water. It is prepared by heating ammonium nitrate, NH_4NO_3, which is readily decomposed into $N_2O + 2H_2O$. It may be obtained commercially, condensed under high pressure in iron cylinders.

Like hydrogen or nitrogen, nitrous oxide when inhaled produces no irritating effects. Although able, outside of the body, to support combustion even better than air, in the body it is unable to maintain the respiratory changes of the tissues. Consequently, nitrous oxide may be administered for only a very short time if it be inhaled pure and free from oxygen.

The possibility of utilizing in practice the inhalation of *pure nitrous oxide* depends upon the fact that, during the very rapid absorption of this gas by the blood, narcosis is produced before suffocation. That nitrous oxide narcosis is not due to this suffocation alone is quite evident from the fact that the typical convulsions due to asphyxia do not occur in warm-blooded animals when it is administered alone, although with complete withholding of oxygen without the action of any narcotic such convulsions would necessarily occur at the end of the first minute.

If a human being be caused to inhale undiluted nitrous oxide with complete exclusion of the air, and the expired air or gases be permitted to escape through a valve, a condition resembling intoxication rapidly develops, and after about one minute the consciousness disappears and anæsthesia and relaxation of the muscles appear at the same time with rather pronounced cyanosis. If now the patient be allowed to breathe air again, the anæsthesia lasts about half a minute longer, and at the end of another half minute recovery occurs rapidly (*Binz*).

It is thus evident that, when pure nitrous oxide unmixed with air is breathed, unconsciousness results at a much less dangerous stage of asphyxia than is the case with pure suffocation (*Zuntz* and *Goldstein*). If animals continue to breathe nitrous oxide after the dyspnœa, which at the start was inspiratory in character, has altered its type to the expiratory one, the convulsions which ordinarily occur during suffocation do not occur, and the animals die as a result of asphyxia, the heart continuing to beat for a considerable period after the respiration has become paralyzed.

The narcotic action of nitrous oxide may be especially well demonstrated on the frog, which is not affected by the lack of oxygen in the atmosphere except after many hours. Although these animals, when kept in an atmosphere of hydrogen for hours at a time, remain reflexly excitable and capable of motion, when placed in pure nitrous oxide they quickly become motionless and no longer react to sensory irritation such as that produced by the application of acetic acid to the skin. If now the frog be again brought into the air, after a few minutes reflex excitability and the motor function return. The very interesting experiments of *Paul Bert*, to which we will soon return again, have clearly shown that nitrous oxide produces a narcotic effect in man even when all elements of suffocation or asphyxia are excluded, provided only that the blood be saturated with a sufficient quantity of this gas.

If *nitrous oxide, diluted with enough oxygen* to prevent suffocation, be inhaled, symptoms are observed which *L. Hermann* thus describes, from experiments made upon himself: "One perceives the

distinctly sweetish taste of the gas, and soon buzzing and drumming in the ears are felt, visual impressions become very indistinct, and there is a feeling of increased warmth and of extraordinary lightness of the limbs, this latter probably being due to the loss of the muscle sense." The muscular movements become very uncertain; there is some depression of the susceptibility to painful impressions and to a less degree to touch. "The flow of ideas is abnormally rapid, and usually there is loud laughing. Consciousness is never completely abolished, and complete anæsthesia also does not occur. If the inhalation of the gas is then interrupted, the normal condition is very quickly re-established."

A complete narcosis does not result from the breathing of nitrous oxide diluted with oxygen, for the reason that the partial pressure of nitrous oxide in a mixture containing 21 volumes per cent. of oxygen is not sufficient to cause the blood to absorb a sufficient amount of this relatively feeble narcotic. For the production of a complete anæsthesia the partial pressure of the nitrous oxide must reach 760 mm. of Hg, one atmospheric pressure. In order to attain this it is necessary either to have the nitrous oxide administered undiluted, —that is to say, under a pressure equivalent to one atmosphere,—and under such conditions asphyxia will quickly follow on the anæsthesia, or, as was first done by *Paul Bert,* 20 per cent. of oxygen is introduced under pressure into nitrous oxide without increasing its volume, and this mixture is administered under a pressure of one and one-fifth atmospheres. This author was able to show that in this fashion it is possible without danger to produce and to maintain a deep narcosis.

However, the actual handling of such narcotic mixtures under pressure is too complicated for every-day use, and consequently nitrous oxide is employed only for narcoses lasting but a very short time, in which case the pure gas is administered, or for light, incomplete anæsthesia, in which nitrous oxide with oxygen is administered. Pure nitrous oxide may be allowed to flow from the cylinder into a rubber bladder from which it is inhaled through a mouth-piece, the expired air escaping through a valve. A simple readjustment of the apparatus permits the administration of air at the end of the first minute. For the incomplete anæsthesias one administers a mixture of 80 per cent. nitrous oxide and 20 per cent. oxygen, the so-called laughing gas, which, under ordinary atmospheric pressure, produces only a condition resembling intoxication, which is entirely free from danger and in which there is a simple clouding of the consciousness with analgesia.

Nitrous oxide mixed with enough oxygen to support the respiration (20–15 per cent.) does not produce complete anæsthesia, because under such a partial tension of four-fifths of an atmosphere the nitrous oxide does not become sufficiently concentrated in the blood. However, in *combination with doses of morphine and scopolamine,* which are

in themselves entirely safe and which alone produce no narcotic effects, the effect of such mixtures of nitrous oxide and oxygen is sufficient to produce a satisfactory anæsthesia. In this way laughing gas may be utilized for anæsthesias lasting for considerable periods and is adapted to major operations (*Neu*). The chief advantages of such anæsthesias are that nitrous oxide produces no irritating effects on the respiratory organs and but slight side actions, and that recovery occurs with unusual rapidity. After cessation of its administration the nitrous oxide content of the blood very rapidly falls below the minimal amount which produces any effect. Animals may become entirely normal within 1–2 minutes after the interruption of the deep anæsthesia produced by this method.

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ETHYL BROMIDE, C_2H_5Br, is a colorless volatile fluid, boiling at 38–39° C. It is readily decomposed under the influence of light and air, and should consequently be kept in brown bottles as nearly full as possible. It may now be obtained in very pure form, but preparations colored brown are not to be used.

ETHYL BROMIDE ANÆSTHESIA has some advantages similar to those of nitrous oxide anæsthesia, for it is much more readily induced and conducted. When a considerable amount—say 5.0–10.0 gm.—of ethyl bromide is poured into the half-closed impermeable mask, the anæsthesia develops extremely rapidly after 10–20 inhalations. If within one and one-half minutes the desired effect has not been obtained, its administration is not to be continued, for this would be attended with considerable danger. When the drop method is employed for the administration of ethyl bromide, the anæsthesia also develops comparatively rapidly, and the stage of excitement is ordinarily comparatively short and the recovery from the narcosis is rapid. After recovery, a taste of garlic in the mouth and a similar odor on the breath, which often lasts for 24 hours or longer, is very disagreeable and disturbing. Vomiting occurs much less frequently than after chloroform.

However, ethyl bromide should not be employed for deep or complete anæsthesia, because the respiratory function is markedly affected by it, cessation of respiration occurring almost simultaneously with the abolition of the reflexes. It is also unsuitable for operations lasting for a considerable period, because the anæsthesia is likely to run along somewhat irregularly, and especially because, as a result of its long-

continued action in the body, secondary disturbances and injury to the internal organs occur to an even greater extent than after chloroform and may produce serious late effects. *Dreser* has demonstrated these late effects in animals.

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HYPNOTICS OF THE ALCOHOL GROUP

Another group of substances, which in their basic actions follow the type of the alcohol group, are used as hypnotics. As such we may use those members of the alcohol group whose behavior in respect to their absorption makes it possible to confine their action to that of the very early stage, and to maintain this first stage for hours. However, a regular and not too rapid absorption and a gradual elimination are not in themselves sufficient to make all the substances of the alcohol group possessing these qualities utilizable as hypnotics, for with many a primary motor excitation produces disturbing effects, and in others harmful side actions on the respiration and circulation or on the metabolism are too readily caused when the therapeutic dose is exceeded.

The pharmacological action of the hypnotics is in all essential points typical of that of the alcohol and chloroform group. With such an hypnotic as chloral hydrate, it is possible to observe and to distinguish all the stages of narcosis when it is administered to higher laboratory animals, such as rabbits. At the start the first thing noted is that the animals move less frequently than usual and react less to psychic impressions. In addition to this action on the cerebrum, even in the first stage, the centres in the midbrain, cerebellum, and medulla, which control motor coördination, are also affected. In the second stage the depression of the cerebrum is more pronounced and the centres of coördination are still more affected, so that the animal is no longer able to rise up but remains lying on the side. In this stage the corneal reflex is diminished, but the respiration is only slightly slowed, while the weakened resistance shown by the animal, when the attempt is made to extend its legs, indicates that the spinal cord, too, is involved in the narcosis. In contrast to the effect of morphine, the animal in this stage reacts more actively to painful stimuli than does a normal one, kicking actively when pinched and raising itself up for a short time. These pain reflexes become feeble only gradually, and disappear only when the corneal reflex is almost completely abolished and when pulling on the extremities no longer excites resistance (*Köppen*). Finally, in the last stage all the reflexes, including the corneal, are completely abolished, the breathing becomes slower, and *death finally results from paralysis of the respiration.*

Side Actions.—With different hypnotics the *blood-pressure* behaves differently in the different stages, and the *respiration* is also affected in different degrees. After choral hydrate, for example, as a result of vasomotor depression, the blood-pressure falls markedly in the second stage at a time when the corneal reflex is still present. The heart-beat is also slowed early and the respiration is distinctly diminished in frequency. With other hypnotics, on the other hand, disturbances of the circulatory and respiratory centres and depression of the heart develop only in the last stages, just a short time before the abolition of the corneal and all other reflexes.

From the above description it may be seen that the complete narcotic action affects the centres in the different portions of the central nervous system, but that, following the general type of the action of the alcohol and chloroform group, *the depression first affects the cerebrum and then the spinal cord, while the vital centres in the medulla are the last to be markedly affected.*

It is only in the first stage of the action of the hypnotics that a condition develops which corresponds to normal sleep. Under their influence dogs fall asleep, assuming their normal sleeping posture, but they may be readily awakened at any time, the muscle tone relaxing as in normal sleep while the breathing is no more slowed than in normal sleep. The only difference appears to be that on waking from such artificial sleep the disturbance of coördination is more marked than on waking from natural sleep, this effect persisting longer than the others after waking. It is only these first grades of their pharmacological actions which are utilized when these substances are employed as hypnotics, the essential factor being the depression of the excitability of certain of the cerebral sensory functions. The hypnotics heighten the threshold for the conscious perception of sensory impressions, this being just what is necessary for

Falling asleep.—Unfortunately, our knowledge of the physiological causation of falling asleep is not satisfactory. Probably the accumulation of fatigue substances, formed during the activity of the nervous system, gradually produces the tendency to fall asleep. When this has occurred, it is under normal conditions sufficient to cause an individual to fall asleep, if the stimuli from the outer world, which are constantly reaching the brain through the organs of sense, are weakened as much as possible. When endeavoring to fall asleep, we darken the room and shut out noises, secure an equable warmth, and free ourselves from uncomfortable clothing,—in short, we purposely cut out all the stronger stimuli which act on the organs of sense, and, as a rule, this is sufficient, for, in the quiet state which precedes the dropping asleep, feebler stimuli no longer reach our consciousness.

Causes of Insomnia.—The essential factor of the so-called essential sleeplessness is an over-excitability of the cerebral cortex, as a consequence of which, normal stimuli, which ordinarily are subliminal, in

spite of the quiet, still reach the consciousness when the attempt is made to go to sleep. Sleeplessness may, however, even with a normal excitability of the cerebral cortex, be due to too powerful stimuli, such as psychical activity, excitement produced by feelings of discomfort, sorrow, etc., which may prevent sleep, or external pathological stimuli, like pain, dyspnœa, cough, etc., may produce the same effects. In such cases, in which severe bodily symptoms interfere with the falling asleep, the sleeplessness is best relieved by removal of these pathological irritations, if this can be done. For example, digitalis will be the best hypnotic if disturbances of the heart be the cause of the sleeplessness. If, however, it is not possible to remove the cause of the pathological stimuli, the prevention of the perception of these stimuli will permit sleep.

In the case of pain, cough, or dyspnœa, this is best accomplished by that specific pain reliever, morphine. In essential sleeplessness, not due to abnormal stimuli but primarily the result of pathological excitability of the cerebral cortex, the hypnotics of the alcohol group are far more useful than the morphine group. On the other hand, in the presence of severe pain, they are effective only in doses large enough to cause a general narcosis of numerous cerebral centres. Such doses may be employed in the presence of extreme degrees of marked cerebral excitement, for example in maniacal patients, and may produce the necessary quieting effect even on the cerebral motor centres. The proof that small doses of hypnotics produce no other effect than to prevent sensory stimuli from reaching the consciousness has been best supplied by *Kräpelin's* experiments in which he tested the effect of various waking stimuli in light sleep and in sleep produced by hypnotics.

INFLUENCE OF HYPNOTICS ON THE DEPTH OF SLEEP

When the brain is over-excitable, one cannot fall asleep, because even the slightest stimuli wake one up. If the drowsy condition of falling asleep has once passed over into a condition of unconscious sleep, under normal conditions the sleep rapidly becomes deeper and, although individuals show marked differences in this respect, the maximum soundness of sleep is usually attained inside of the first hour. Systematic experiments, in which it was determined what intensity of noise was sufficient to wake the subject up after he had been asleep for a definite period of time, have shown how great are the differences in the soundness with which different persons sleep. The height of the waking threshold during a certain period of sleep may be used as the measure of the soundness of sleep. If now these waking threshold values are expressed in curves, sleep curves for the different periods of the experiment may be obtained which indicate graphically the more or less rapid rise to the maximum soundness of sleep and the gradual fall up to the time of awaking (*Kohlschütter*).

With good normal sleep the summits of the curves are higher and are more rapidly attained than with poor sleep, in which the curve expresses an insufficient soundness of sleep during the first hours and then runs along at about the same moderate height, instead of falling in the morning as an expression of the awakening in a refreshed condition. Under the influence of an hypnotic, for example, of paraldehyde, a light and insufficient sleep is induced which approaches the type of normal sleep.

In Fig. 7 the curves obtained by *Michelson* by observations, under as constant conditions as possible, on afternoon sleep lasting several hours, with and without paraldehyde, are given as evidence of this. The two curves, *IIa* and *IIb*, which were obtained under the influence of paraldehyde, in comparison with curve *I*, the curve of normal light afternoon sleep, show a much more pronounced soundness of sleep, as they rise much more sharply and thus resemble the type of normal sleep during the night.

The results of investigations of simple psychical reactions in individuals, who had taken some hypnotic, are in complete agreement with this demonstration that these hypnotics diminish the efficiency of waking stimuli, for *Kräpelin* and his collaborators have shown that an impairment in the perception of external stimuli is a characteristic effect of the hypnotics (paraldehyde, chloral hydrate, trional), which is also produced by alcohol. Small doses of morphine do not produce this effect on the function of perception, and consequently they are not to be considered as true hypnotics.

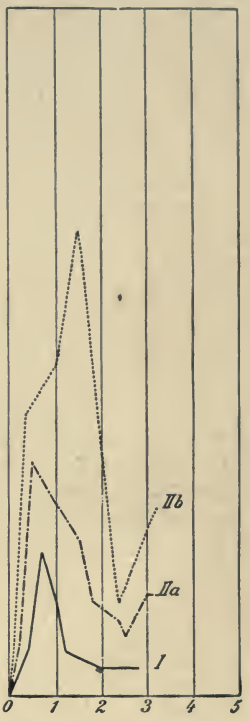

FIG. 7.—*I*, curve indicating depth of sleep in an afternoon nap lasting several hours; *IIa*, *IIb*, curves obtained under paraldehyde, conditions otherwise similar.

In addition, the different hypnotics, although in very varying degrees, also render more difficult the initiation of motor nervous impulses. While paraldehyde and particularly alcohol impair motor functions only after large doses, and in smaller doses act as motor stimulants, chloral hydrate and trional, from the very start, in addition to impairing the perception of sensory impressions, show a tendency to produce a quieting of the motor functions (*Hänel*). Consequently these latter have the power of producing a pure hypnotic effect without any disturbing symptoms of intoxication, while alcohol may only in a limited sense be described as a hypnotic, for the primary motor excitement, caused by it in many individuals, produces waking stimuli and thus prevents the falling asleep.

IMPORTANCE OF THE RATE AT WHICH HYPNOTICS ARE ABSORBED AND ELIMINATED

This cutting out of external stimuli by the hypnotics produces the essential conditions for the development of sleep. As in neurasthenics the inability to fall asleep, except late and with great difficulty, is often the chief disturbing symptom, in these cases the most important desideratum is to deepen the sleep at the very start. Consequently, the readily absorbable hypnotics, chloral hydrate, paraldehyde, and the like, are the best means of helping such patients to fall asleep. With other forms of disturbed sleep, for example, in the typical disturbance of sleep commonly met with in the aged, the patient falls asleep easily

enough, but soon after wakes up again, and then cannot sleep again. With insomnia of this type hypnotics possessing a more lasting action are indicated, for example, trional, which *Hänel* was able to demonstrate caused a diminution in the power of perception which persisted into the following day.

In general it is essential for hypnotics that their action be rapidly produced and persist for a sufficient period. Both of these desiderata will be best accomplished by substances which are soluble in water, which distribute themselves equally in the stomach contents, and which, after gradual passage into the intestine, are gradually absorbed. At the same time hypnotics must not be excreted or destroyed too rapidly, while, on the other hand, a too slow excretion or destruction is also undesirable, because under these conditions the effects would persist on the following day, as has often been observed after the administration of sulphonal and trional, as also after veronal.

Freedom from Harmful Side Actions.—Above all, however, all hypnotics should, in therapeutic doses, produce no dangerous side effects on the circulation, respiration, or metabolism, and also should not disturb the stomach. With the augmentation or frequent repetition of the dose, naturally all hypnotics are dangerous. In the presence of an especial individual susceptibility or of pathological conditions,—*e.g.*, cardiac or pulmonary disease,—these side actions, especially in the case of the more powerful hypnotics, may be produced even by the doses which are necessary in order to produce sleep. This is the case, however, to an even greater degree with those larger doses of hypnotics which are employed in conditions of psychic excitation, with the object of exerting a sedative effect on the cerebral motor centres, or which are used as antidotes in poisoning by convulsant poisons, or in tetanus, etc., in order to depress the excitability of the spinal cord.

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CHLORAL HYDRATE

Chloral hydrate is the member of this group which has been longest in use. It occurs in the form of dry transparent crystals with an irritating odor and a mildly bitter and pungent taste. It is very soluble in water, alcohol, and ether, and is quite hygroscopic. Concentrated solutions strongly irritate the mucous membranes, and consequently this drug should always be administered sufficiently diluted and never in solid form, otherwise its irritating action on the stomach mucous membrane may cause discomfort.

Chloral hydrate is formed of chloral and one molecule of water. Chloral itself, $CCl_3.COH$, or trichloracetaldehyde, the aldehyde of trichloracetic acid, is a colorless corrosive fluid. It was first prepared by *Liebig*, in 1832, by the action

of chlorine on ethyl alcohol, the method still used in its manufacture. Chloral unites with water with the development of heat to form chloral hydrate, the equation of the reaction being $CCl_3.COH + H_2O = CCl_3.CH(OH)_2$. According to *Victor Meyer* and *Caro*, this water is not combined as water of crystallization, but is a dihydroxyl combination, for, in contradistinction to chloral, it no longer contains an aldehyde radical.

The reaction between chloral hydrate and aqueous solutions of the alkalies is of particular interest. Chloral is decomposed by the alkalies, with the formation of chloroform and formic acid, a reaction which takes place at ordinary temperatures and still more readily under the influence of heat, according to the following formula:

$$CCl_3.COH + KOH = CHCl_3 + HCOOK.$$

It is this decomposition of chloral with the formation of chloroform which in 1869 suggested to *Liebreich* the hypothesis that chloral hydrate was gradually broken up by the alkaline reacting blood, with the formation of chloroform, and that thus a continuous chloroform effect would be exerted in the body. While this hypothesis has been shown to be incorrect, it was responsible for the introduction into therapeutics of the first synthetically formed hypnotic.

As a matter of fact, chloral hydrate is *not decomposed* in the body, but produces its effects as unchanged chloral. This is shown by the fact that almost all of it is excreted undecomposed but in combination with various substances. Furthermore, the carbonate alkalinity of the blood is not sufficient to decompose chloral hydrate at the body temperature in the manner in which this decomposition occurs in the test-tube.

Moreover, in case such a decomposition of chloral hydrate took place in the body to any recognizable extent, chloroform would necessarily be present in the expired air, but, according to *Hammarsten, Hermann,* and *Tomascevicz*, even the most delicate reagents fail to indicate its presence here. Chloroform is also not present in the blood of chloralized animals, although chloral hydrate may be demonstrated therein in all periods of the narcosis (*Archangelsky*).

FATE IN THE BODY

Chloral hydrate, as already mentioned, is almost completely excreted in the urine, chiefly as trichlorethylglycuronic acid or urochloralic acid, and only in very small amounts as unchanged chloral hydrate. A very small portion is retained in the body for a considerable time and is gradually decomposed, with a resulting increase of the chlorides in the urine, which persists for some time (*Liebreich*, 1869).

During its transformation into urochloralic acid, which is pharmacologically inert, chloral, which is a halogen substituted aldehyde, is first reduced to an alcohol before combining with glycuronic acid. The combination of chloral with glycuronic acid is thus seen to be a process similar to that by which numerous substances of the aliphatic series, and particularly aromatic substances, are distoxicated (*Musculus u. Mering, Külz*).

This combination of drugs with glycuronic acid is of some importance to the practising physician, inasmuch as some of these combinations, for example urochloralic acid, reduce cupric oxide in alkaline solutions. Urine containing

such combined glycuronic acid may consequently give a reaction which might lead to an erroneous conclusion that they contain sugar. Glycuronic acid is, however, not fermented by yeast and in combination polarizes light to the left.

THERAPEUTIC EMPLOYMENT.—As a rule, in doses of 1.0 gm. for an adult, chloral hydrate produces sleep, and in doses of 2.0–3.0 gm. causes profound sleep. As a result of its ready solubility and absorbability, sleep usually follows very promptly on its administration, lasts about 8 hours, and is usually not followed by any after-effects. In some individuals exanthematous eruptions are caused by chloral, while in others the local irritating effect in the stomach causes gastric disturbance. Idiosyncrasies toward it may also be met with, as a result of which it fails of producing hypnotic effects and, in place of so doing, even causes considerable excitation. Consequently, the first dose of this drug should not exceed 1.0 gm. (*Stintzing*).

Much larger doses, exceeding even the ordinary maximum dose of 3.0 gm., may be necessary to produce the desired sedative effects in conditions of mental excitement, in delirium tremens, or in the convulsions of eclampsia, tetanus, or strychnine poisoning. With such doses, however, the dangerous actions of this drug may manifest themselves to a very appreciable degree.

These HARMFUL ACTIONS OF CHLORAL HYDRATE consist chiefly in harmful effects on the *heart* and on the *vessels*. Inasmuch as its actions, in general terms, resemble a protracted mild chloroform action, the vasomotor centres and the heart are depressed relatively early, just as is the case with chloroform. In patients with fatty hearts, myocardial degeneration, arteriosclerosis, etc., these dangerous actions may manifest themselves even after ordinary hypnotic doses, and after large doses sudden heart death may occur in such patients. Like chloroform, chloral hydrate, even in therapeutic dosage, may cause a fall in the blood-pressure as a result of a commencing vasomotor depression, and the pulse may become soft with increased amplitude. The differences between the therapeutically effective concentrations in the blood and the concentrations which depress the circulation are not great. In *Archangelsky's* experiments the chloral concentration of the blood of dogs lying in profound sleep lay between 0.03 and 0.05 per cent., while when this concentration reached 0.056 per cent. the blood-pressure had fallen to one-half of its original height, and with a concentration of 0.07 per cent. cessation of respiration occurred. [Clinical experience with this drug indicates very clearly that the dangers of harmful depression of the circulation, when chloral is correctly used, have been greatly over-estimated. The figures quoted above of a concentration of 0.03–0.05 per cent. in the blood, in no way correspond to the concentrations which can be produced by any ordinary doses.—TR.]

Relaxation of the vessels results in a slowing up of the blood flow throughout the body, and, if this lasts for any considerable time, in

patients with respiratory disturbance it may lead to cyanosis and even œdema of the lungs, while, in addition, the decided direct depression of the respiratory centre produced by chloral hydrate warns one to exercise caution in its use in such patients.

With continued use there is danger of habituation. Another reason why abuse of this drug is dangerous is that chloral hydrate may cause a parenchymatous degeneration of certain of the important organs, in which particular its effect is similar to that of prolonged chloroform anæsthesia.

When this occurs, the decomposition of proteids is augmented, just as occurs in phosphorus poisoning. However, the breaking down of the proteids does not proceed to the normal final stages, but stops with the formation of some more complicated intermediate decomposition products, whose nature is still unknown but which are probably substances resembling the peptones (*Harnack*).

Toxicology.—Especially when first introduced into practice numerous acute medicinal poisonings by chloral hydrate resulted from its administration in too large doses, and, as a result of its continued use as a sedative, cases of chronic chloral habit developed, particularly in insane asylums. To-day medicinal poisonings have become far less frequent, but it is frequently employed for suicidal purposes. Cases of fatal poisonings have been observed after doses not exceeding 4.0 gms.

Acute Poisoning.—The symptoms of acute poisoning correspond in general with those of too deep anæsthesia and coma, which have already been described in connection with poisoning by other narcotics. In these cases the symptoms of insufficient respiration and marked impairment of the circulation develop early and the body temperature falls. If the drug be very rapidly absorbed, death may ensue very quickly as a result of a direct paralytic effect on the heart, and the patient may suddenly collapse. When the absorption has taken place more gradually, coma and complete anæsthesia with abolition of the reflexes develop, and death results from cessation of the respiration, the heart action also being extremely feeble. In contrast to the usual behavior of the pupils in morphine poisoning, they are widely dilated in chloral poisoning, and, with equally deep coma, the circulation is much more markedly depressed by chloral hydrate, while the respiration remains relatively good much longer than is the case in morphine poisoning, in which the respiration is alarmingly depressed before the circulation is markedly affected.

The treatment of acute chloral poisoning consists first in removing the poison by washing out the stomach. Emetics cannot be used for this purpose, for they will necessarily fail to act, on account of the depression of all reflexes, including those which bring about emesis. In severe poisoning artificial respiration must be instituted. As long as this is not necessary the effort is made to maintain the

functions of the vasomotor and respiratory centres by various stimulating agents. For this purpose one uses, as in other narcotic poisonings, sensory stimuli, subcutaneous injections of solutions of caffeine, preparations of camphor and of atropine. [Caffeine, in the form of strong hot coffee by mouth and by rectum, is used almost as routine. Strychnine subcutaneously appears also to be of distinct value, and epinephrin intramuscularly or intravenously, as also heat, certainly appears to be indicated.—Tr.]

Chronic Poisoning.—In chronic chloral poisoning disturbances of the digestive organs of most various nature, as well as vasomotor and psychical disturbances, occur. Affections of the skin are also very common. In general, the clinical picture resembles that of chronic morphinism. When the attempt is made to give up the drug, various uncomfortable symptoms and disturbing conditions develop, among them great nervousness, anxiety, and insomnia.

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OTHER HYPNOTICS OF THIS GROUP

The various disadvantages of chloral hydrate soon made it desirable to search for substitutes with similar hypnotic action unaccompanied by the undesirable side actions, and, as a result, the number of hypnotics of the alcohol group, which have been introduced and which are still widely used, has become extremely large. This is in itself evidence that none of these hypnotics is ideal, possessing all the properties wished for. With some, the disagreeable taste and odor,—*e.g.*, paraldehyde,—with others, unfavorable behavior in respect to absorption and excretion,—*e.g.*, sulphonal,—are unavoidable drawbacks. Still others possess the disadvantage that when repeatedly administered habituation readily develops, while with others harmful side actions occur when they are used continually.

On the other hand, the different types of insomnia and the variable individual susceptibility toward the different drugs are responsible for the practical demand for numerous hypnotics, for the undesirable side actions of the different hypnotics are of greater or less moment according to varying pathological conditions in which they may be employed. Furthermore, the harmful effects of the continued use of one drug often render it necessary that a change be made from one hypnotic to another.

If one surveys the whole group of hypnotics which have been introduced since chloral hydrate, the empiric rule may be formulated that those hypnotics which contain no halogen, in general, affect the heart and the vessels less than do those containing these elements. This conclusion corresponds entirely with that formed from practical experience with the general anæsthetics. As a result, with the halogen-free hypnotics there is a greater difference between those doses sufficient to produce sleep and those which unfavorably affect the circulation and respiration.

Chloralamide.—Substitutes for chloral hydrate, which contain the molecule of this uncommonly active substance in combination and from which the chloral may be set free in the body, will consequently possess no essential advantages over chloral hydrate itself. This holds true for the widely used chloralamide, which is formed by the union of chloral with formalin according to the following formula:

$$CCl_3.CHO + H.CONH_2 = CCl_3CH(OH)N(CHO)H.$$

This drug occurs as crystals, soluble in water in the proportion of one part in 20, which are not irritating and which possess a slightly bitter taste. The absence of irritating action in the stomach and the slight taste are the chief advantages which it possesses as compared with chloral hydrate, but the effective hypnotic dose is one and one half times as large as that of chloral. Sleep is usually produced from ½ to 2 hours after its administration.

Dormiol.—Another combination of chloral with dimethylethylcarbinol (amylene hydrate), dormiol, has recently been introduced and recommended (*Fuchs u. Koch*). This amylene chloral is an oily water-clear fluid with a smell resembling that of camphor. It may be administered in gelatin capsules containing 0.5 gm. In dosage of 0.5–1.5 gm. it induces sleep after ½ to 1 hour, which is not accompanied by harmful side effects (*Peters*). [Later experience with this drug has shown that this claimed freedom from harmful side actions has not been justified.—Tr.]

Isopral.—Another hypnotic containing chlorine, isopral, or trichlorisopropyl alcohol (*Impens*), has been rather widely used. This drug is readily soluble and easily absorbed, sleep usually following in ¼ to ½ hour after its administration in dosage of 0.5 to 1.0 gm. (*Urstein*). Although its toxic action on the heart is slight, experiments on animals show that it, too, depresses the blood-pressure. Caution is consequently necessary in connection with its use in the presence of circulatory disease. [*Hatcher* has demonstrated that the claims made for its relatively slight toxicity as compared with chloral are not correct.—Tr.]

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Paraldehyde.—The first hypnotic of this group which is really free from harmful side actions on the functions of other organs was introduced by *Cervello* in 1883. [This freedom from harmful actions

is only a relative one.—Tr.] This is a polymeric modification of the common aldehyde $CH_3.COH$, three molecules of which are combined in it.

It is a clear, colorless, readily inflammable fluid with a characteristic odor and burning taste, rather soluble in water (1 to 8), and easily absorbed, so that sleep quickly follows its administration, often within 10 to 15 minutes. It is a powerful narcotic, with little harmful action on the respiration, circulation, or metabolism. In essential insomnia, doses of about 3.0 gm. are usually efficacious, and even with long-continued employment of such doses no dangerous side effects result. [This statement is not strictly correct, for the literature contains more than one reference proving that the contrary may at times be true.—Tr.] In extreme insomnia the dosage must be increased up to 4–6 gm., but much larger doses (even as much as 30–60 gm.) have been taken without dangerous results (*Bumke*[1]). According to many observers, habituation to paraldehyde is readily acquired, just as is the case with alcohol, but this certainly is not always the case (*Bumke*,[2] *Stintzing*). The only disadvantage of this relatively harmless and efficient drug is its disagreeable taste, which is best disguised by red wine or tea, and its odor, which resembles that of fusel oil, and which, on account of its slow excretion by the lungs, is apparent in the breath even on the day following its administration.

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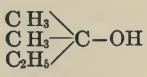
Stintzing: Penzoldt-Stintzing's Handb. d. Ther. d. inn. Krankh., vol. 5, p. 396.

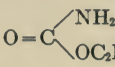
Amylene hydrate, dimethylethyl carbinol, is a tertiary alcohol of the amyl series —



It is a colorless, oily, rather soluble (1 to 8) fluid, with a disagreeable odor resembling that of paraldehyde. In respect to the intensity of its hypnotic power it lies between chloral hydrate and paraldehyde,—1.0 gm. chloral hydrate = 2.0 gm. amylene hydrate = 3.0 gm. paraldehyde. Like other amyl compounds, such as the so-called fusel oils, which in general exert a more powerful effect on the nervous system than the ethyl combinations,—*e.g.*, ethyl alcohol,—amylene hydrate also produces more marked depression of the circulation than does paraldehyde. However, in this respect amylene hydrate has the reputation of being less open to objection than choral. The usual dose is 2.0 gm., 4.0 gm. being the maximal single dose. It may be administered in gelatin capsules or in solution by mouth or by rectum. This drug possesses the disadvantage that even hypnotic doses may cause a condition resembling alcoholic intoxication, as it strongly excites the motor centres, so that in animals restlessness or even severe convulsions may result from its administration in poisonous doses (*Harnack u. Hermann Meyer*).

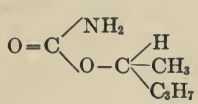
Urethan is satisfactory in respect to its freedom from disagreeable side actions, as well as in respect to its solubility, taste, and odor. In experiments on animals it shows itself to be an extremely good hypnotic which even in strongly hypnotic doses does not impair the heart action at all (*Schmiedeberg*). Its hypnotic power in man is, however, weak and uncertain, so that it has not been able to establish itself as useful.

Chemically it is the ethyl ester of carbaminic acid—



It occurs as colorless and odorless crystals readily soluble in water, with a salty taste. For adults the dose is 2.0–4.0 gm.

Hedonal.—Under the name of Hedonal, *Dreser* has introduced another hypnotic belonging chemically to the same class as urethan. In it the ethyl radical is replaced by a methylpropylcarbinol radical



It occurs as colorless crystals, soluble with difficulty in water, and with a somewhat disagreeable taste resembling that of peppermint. It is best administered in powdered form in wafers, and, in doses of from 1.0–2.0 gm., produces a much more powerful hypnotic effect than ethyl urethan (urethan). This drug has been highly praised by some authors, but, according to *E. Müller*, it appears to be unreliable in cases of slight insomnia and often to fail even when larger doses are given. It appears to have no dangerous side actions, but at times a pronounced polyuria caused by it interferes with the sleep. It also appears that habituation readily occurs with both hedonal and urethan.

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SULPHONAL and TRIONAL have apparently been more widely employed as hypnotics than almost any other drugs. The hypnotic actions of these disulphones was accidentally discovered by *Baumann* and *Kast* in certain physiological experiments instituted with another object.

Chemically sulphonal (sulphonmethane, U.S.P.) is diethylsulphonedimethylmethane, $(CH_3)_2 = C = (SO_2C_2H_5)_2$, and occurs as colorless, tasteless crystals, very slightly soluble in cold water (1 to 500). When administered as a powder in doses of 1.0 to 2.0 gm. (4.0 gm. [? TR.] maximal single dose) together with a sufficient quantity of warm fluid, sleep usually results after the lapse of 1–2 hours. On account of its relative insolubility, its effects are produced not only slower than is the case with other hypnotics, but they last longer, on account of the slowness with which it is decomposed and excreted. After waking there is slight dizziness, and on the following day the patient is often drowsy.

Trional and tetronal are analogous substances, in which ethyl radicals replace one or both of the methyl groups of sulphonal and which are more active than their mother substance.

TRIONAL (diethylsulphonemethylethylmethane), or sulphonethylmethane, is at present preferred by most authorities to sulphonal, because, as it is more soluble than sulphonal, sleep is more rapidly

induced, and because the factors determining its decomposition and elimination are more favorable (*Morro*). Doses of 1.0–1.5 gm. cause sleep after ¼ to ½ hour. 4.0 gm. [? Tr.] is the maximal single dose.

In proper doses sulphonal and trional produce no harmful effects on the circulation, respiration, or digestion. After larger doses or after continued use of small doses, however, they may cause poisoning, evidenced by disturbances of the digestive organs, the metabolism, and the central nervous system. Single doses produce such symptoms of poisoning only when the usual dose has been very largely exceeded. This holds true especially for the relatively less poisonous trional (*Kobert*).

Trional, like sulphonal, often produces a satisfactory hypnotic effect even in the second night, this after-effect proving that a certain quantity of the drug still remains in the body in a form which is still active. The harmful effects of both of these drugs also are due to this persistent after-effect, the danger of cumulation being greater with the less readily decomposed sulphonal than it is with trional. The majority of the numerous cases of poisoning produced by these drugs, which formerly were frequently observed as a result of their careless employment (especially with sulphonal), occurred when they were administered during too long a period (*lit. Friedlander, v. Taylor* and *Sail*).

Kast states that in man the dosage of sulphonal should not exceed 2.0 gm., and in women, who are much more readily poisoned, it should not exceed 1.0 gm., and that, when used for a long time, its administration should be discontinued in periods of one to several days. With trional also daily administration is not permissible, and even with men the doses should not exceed 1.25 gm.

In SULPHONAL POISONING the symptoms consist in persisting confusion, ataxia, constipation, vomiting, and abdominal pain, and also in symptoms of irritation of the kidney, albuminuria and nephritis. In the majority of cases there is also a peculiar decomposition of the hæmoglobin, resulting in the appearance of hæmatoporphyrin in the urine. The reddening of the urine thus caused, while not constant, is a very frequent symptom of sulphonal or trional poisoning, and, as this symptom is often one of the first to develop, it may serve as a warning. Consequently, whenever these drugs are continually administered, the urine should be regularly examined. Thus far we know nothing of the manner in which hæmatoporphyrinuria is produced. It may be experimentally produced in rabbits but not in dogs (*Neubauer*).

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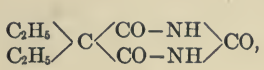
VERONAL.—Comparatively recently, diethylbarbituric acid, veronal, and dipropylbarbituric acid, proponal, have been introduced as hypnotics and have very rapidly been extensively employed (*E. Fischer* and *v. Mering*).

Veronal,



occurs as a crystalline powder, soluble with difficulty in water, and with a slightly bitter taste. The mean hypnotic dose is 0.5 gm., but with women doses of 0.25–0.3 gm. are often sufficient. As far as may be judged from the reports at present available, it is a reliable and, in proper dosage, harmless hypnotic. However, it appears that its use is not unattended with danger in case its administration is too quickly repeated. [*At least two fatal cases of poisoning have occurred after relatively small amounts had been taken.*—TR.] It is excreted in unaltered form, but rather slowly (*E. Fischer* and *v. Mering, Aug. Hoffmann*), so that prolonged action and rather lasting conditions of confusion have often been observed. Its sodium salt, *medinal*, is more soluble in water, and consequently may at times be preferred to veronal. When injected subcutaneously into animals, from 45 to 90 per cent. of the amount administered is excreted in the urine, the amount thus excreted varying with the size of the dose. It has not been possible experimentally to demonstrate that it produces any well-marked cumulative effects (*Bachem.*) Following too large doses in a number of cases, sleep lasting for days has already been observed. [In animals veronal may produce degeneration of the kidney.—TR.]

Proponal acts more rapidly than veronal, and 0.35 gm. appears to produce about the same effect as 0.5 gm. of veronal (*Römheld*). *Ziehen* warns against exceeding the dose of 0.5 gm.

Neuronal.—Still another hypnotic is neuronal, bromdiethylacetamide, $CBr(C_2H_5)_2CONH_2$ (*Fuchs* and *E. Schultze*). This is a powder, soluble with difficulty in water, which is effective in doses of from 0.5-1.0 gm. Up to 1905 there were no reports indicating that it produces any harmful side effects or cumulation (*Bleibtreu, K. Schultze*).

Bromural.—*Krieger* and *v. d. Velden* have reported favorably of their experience with bromural, 2 monobrom-isovaleryl-urea, in doses of 0.6–1.0 gm. in the form of tablets. This drug acts as a mild hypnotic and useful sedative, producing its effects fairly rapidly. In experiments on animals a deep narcosis may be induced by this drug without harmfully affecting the circulation or the respiration.

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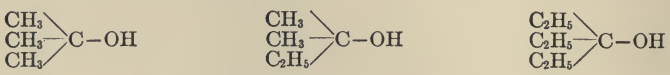
THE RELATIONSHIP BETWEEN CHEMICAL CONSTITUTION AND PHARMACOLOGICAL ACTION

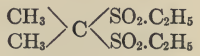
In this section only those members of the alcohol group have been discussed which have been widely employed as anæthetics or hypnotics. There is a very much larger number of substances of the alipathic series which possess more or less marked pharmacological actions of this nature, and consequently, as may well be understood, many attempts have been made to determine the relation between the constitution of these hydrocarbons, alcohols, aldehydes, ketones, sulphones, esters, etc., and their pharmacological actions. As a result, a number of laws or principles have been discovered, with the aid of which it has been possible to make certain deductions which have rendered possible a successful search for new active substances.

In general, substances in which the alkyl radicals are attached to tertiary or quaternary carbon atoms are more active than the analogous combinations containing the carbon combined with only one or two other carbon atoms. For this reason, the primary alcohols produce less narcotic effect than the secondary ones, and these in turn less than the tertiary alcohols (*v. Mering* and *Schneegans*). Further, in general the law holds good, that ethyl groups, if attached to carbon, endow substances with more pronounced narcotic properties than do methyl groups in the same situation. Thus, for example, ethyl alcohol is more strongly narcotic than methyl alcohol. *v. Mering* and *Schneegans* have found that in the series of tertiary alcohols

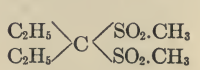


trimethyl carbinol, dimethylethyl carbinol, and triethyl carbinol, the hypnotic action increases according to this law, the hypnotic dose in rabbits for these three substances being respectively 4.0, 2.0, and 1.0 gm. *Baumann* and *Kast* have shown a similar relationship between the narcotic power and the number of the ethyl radicals contained in the molecules of the members of the sulphone series, in which the attachments of alkyl radicals to the sulphone radicals which are attached to the quaternary carbon appear to have the same significance as their direct attachment to the carbon atom.

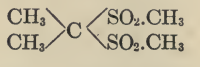
Sulphonal



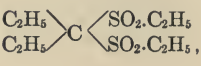
is consequently approximately as active as dimethylsulphonediethylmethane



The analogous substance containing only methyl groups, dimethylsulphonedimethylmethane,



is inactive, but, on the other hand, trional, which contains three ethyl radicals, is more active than sulphonal, while tetronal, diethylsulphonaldiethylmethane,



which contains four ethyl groups, is still more active. This relationship between the activity of the substance and the number of ethyl groups holds good, however, only for a certain intramolecular arrangement of the atoms, such as is present in sulphonal. Even in such disulphones as contain the sulphone radical attached to different carbon atoms, as, for example, in ethylenediethylsulphone,

$$\begin{array}{l} CH_2-SO_2.C_2H_5 \\ | \\ CH_2-SO_2.C_2H_5, \end{array}$$

the ethyl groups no longer produce these effects (*Baumann* and *Kast*).

This law, therefore, holds good only within certain limits, the introduction of other groupings into the molecule lessening the importance of the ethyl radicals or entirely abolishing it. Notwithstanding this, the deduction that the combination of ethyl groups with a tertiary or quaternary carbon atom results in especially powerful hypnotic powers, has pointed out the path to the synthesis of other hypnotics,—for example, to that of veronal (*Fischer u. v. Mering*).

The introduction of halogen atoms attached directly to carbon increases the narcotic power of substances already possessing such powers. Thus, the narcotic effect of the hydrocarbon methane, CH_4, is extremely slight, but, with the successive substitutions of chlorine for its hydrogen atoms, its narcotic action is augmented, chloroform, $CHCl_3$, being more active than bichlormethane, CH_2Cl_2, which in turn is more active than methylchloride, CH_3Cl. However, the introduction of chlorine atoms, as a rule, also endows the substance with toxic side actions on the heart and vasomotor centres, a fact to which attention has already been directed in connection with the comparison of ether with chloroform, and also in connection with the comparison of chloral hydrate with alcohol and the chlorine-free substitutes for chloral hydrate. As a result of the study of these relationships, it is clearly evident that not only the intensity of the narcotic actions but also the character or quality of pharmacological actions may be changed by the introduction of chlorine atoms (*Kionka*). For example, the introduction of still another chlorine atom into chloroform transforms this substance into tetrachlormethane, CCl_4, which is a convulsant poison (*v. Ley*). The strengthening influence of the introduction of the halogens may also be demonstrated when bromine atoms are substituted in hydrocarbons (*Fuchs u. Schultze, v. d. Eeckout*).

The narcotic power of trichloracetic acid when compared with that of the corresponding aldehyde, chloral, is very slight. This will serve as an illustration of the general law that the introduction of acid radicals weakens or abolishes the narcotic activity of various atom groups.

The investigation of the relationship between chemical constitution and pharmacological action in the alcohol group has thus led to the conclusion that the entrance of certain atoms and atom groups into certain active compounds augments or weakens their activity. There is still lacking, however, an explanation why the ethyl groups, for example, increase the activity of the substances only when they are introduced into substances of certain definite configuration and do not augment the activity of other molecules with another configuration. It is certain that the ethyl groups themselves do not independently produce these effects, for those substances whose activity is attributable to the ethyl groups—such, for example, as the disulphones (*Diehl*) or ethyl alcohol—certainly produce their effects before, and not after, they have been decomposed. The ethyl groups, therefore, do not produce their pharmacological effects after they have been split off from the whole complex. If, therefore, the number of them present in the molecule determines the degree of its activity, this is only to be

understood on the assumption that the entrance of the ethyl groups into the molecule endows it with certain chemical or physical properties which are responsible for the narcotic action. This also holds true for the augmentation of physiological activity resulting from the introduction of halogen atoms, for chloroform during narcosis is excreted almost entirely in unaltered form, being decomposed scarcely at all in the body. The setting free of chlorine, therefore, cannot be the cause of this so strikingly augmented physiological activity of chloroform as compared with its chlorine-free mother substance, methane.

An instructive example of these relationships is also presented by the halogen substitution products of isovalerylurea. In the cold-blooded animals the chlorine, bromine, and iodine substitution products of this substance are much more strongly narcotic than is the halogen-free mother substance. As, however, the halogen is present in a sufficiently firm combination only in the chlorine and bromine substitution products, and as the iodine substitution product is decomposed and rapidly loses its iodine at the temperature of warm-blooded animals, this last combination behaves quite differently in the warm-blooded animals than do the other two, being no more active at this higher body temperature than is the halogen-free mother substance (*v. d. Eeckhout*). It is thus clear that the halogen in the molecule augments its activity only so long as it is able to influence the properties of the whole atom complex.

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THEORY OF NARCOSIS

A theory of narcosis formulated by *Hans Meyer*[1] and *Overton*, which may now be discussed, permits us to determine which physical or chemical properties of the narcotics are responsible for their activity and to learn in what fashion these properties are modified by the presence of certain radicals in the molecule.

As early as 1876, *Buchheim*[1] defined the aim and task of pharmacologists as consisting, first, in determining at which point in the body a drug acted, and, second, in explaining such actions by a reaction between the cell constituents and the drug. This second problem, that of showing how the pharmacological actions are due to the properties of the chemical substances which produce them and to their action on

the cells affected, has, up to the present time, been successfully solved in a few instances only, of which carbon dioxide poisoning is one. Conditions similar to those involved in the reaction between carbon dioxide and hæmoglobin may also be assumed to explain the elective action of curarine and other ammonium bases on motor nerve-endings (*Führer*). However, the formation of a chemical combination between the drug and some constituent of the protoplasm, which (after the analogy with the action of carbon dioxide) we are justified in assuming, may in many instances be assumed only in the case of such foreign substances as are chemically active.

Among the narcotics of the aliphatic series, on the other hand, there are many chemically entirely inactive substances which exert a characteristic narcotic action on the nervous system. If we wish to learn which of their properties are responsible for the pharmacological actions exerted in common by the narcotics of this series, which in their chemical behavior differ from each other so decidedly, we must look for those properties common to all of them,—to those among them chemically least active, for example, the saturated hydrocarbons; as well as to those chemically most active, for example, the aldehydes, such as choral hydrate.

Lipoid Solubility.—It has been found that all possess the physical property of being soluble in both water and fats. This especial solubility in fats, associated with a sufficient solubility in water, is essential for the absorption of the narcotics by the cells and is responsible for their peculiar distribution in the different tissues of the body, and by the physical-chemical theory of narcosis explains the pharmacological action of the narcotics.

As early as 1847, shortly after the discovery of ether and chloroform anæsthesia, *Bibra* and *Harless* sought to explain their anæsthetic power as the result of their power of dissolving fat. As a result of quantitative determinations of the fat contents of normal and narcotized animals, they believed that they had found out that the anæsthetics actually removed larger or smaller quantities of fat-like substances from the brain. They assumed, consequently, that these drugs were responsible for a sort of extraction of fat-like substances from the brain, and considered that this was the cause of anæsthesia.

However, there can be no question of such extraction of the fat-like constituents of the nerve-cells, for this would be inconsistent with the characteristic rapid restoration of function which follows interruption of anæsthetization.

Hermann investigated the hæmolytic action of ether, chloroform, etc., and explained this by their power of dissolving the lecithin of the red blood-cells, and drew a parallel between this and the narcosis of the central nervous system with its large content of lecithin.

These two hypotheses, therefore, contained the correct central idea of explaining the narcotic action of various drugs by their common

property of ready solubility in the fats, for they produce their effects on the central nervous system because they go into solution in the fat-like constituents, the lipoids, of nervous tissues, and form a physical-chemical combination with them.

Elective Absorption by the Nervous System.—Long ago, *Buchheim* [2] stated clearly that the pharmacological actions affecting chiefly the nervous system were to be considered as the result of reactions with those cell constituents "which are peculiar to the nervous system or which occur chiefly there." As a matter of fact, the central nervous system differs from other tissues especially in the large quantity of its fat-like constituents. A substance foreign to the body, moreover, can produce a pharmacological action only where it is absorbed in sufficient quantities by the cells. Consequently, a necessary primary condition for the elective action of the narcotics on the nervous system is its sufficient absorption by the functional elements. Narcotic substances must first of all be neurotropic, in the sense in which this expression was first employed by *Ehrlich.*

Ehrlich [1] was the first to attribute the absorption and storing up of various substances by the nervous system to their affinity to its lipoid constituents, and especially to emphasize the importance of studying the distribution in the body and in various organs of pharmacologically active substances. For such investigations he employed chiefly dyes, the distribution of which is so readily apparent after intravital staining or so readily demonstrable by various reactions. Starting with these ideas, he demonstrated that the majority of the basic dyestuffs, which are absorbed by the brain, are also stored up in various other fatty tissues. Neurotropism and lipotropism thus go hand in hand. If now a sulphonic acid radical was introduced into a neurotropic dyestuff, its distribution in the body was found to be entirely altered, the dyestuff losing its neurotropic properties as a result of the introduction of the acid radical; and *Ehrlich* drew the parallel between this observation and the fact that neurotoxic substances, such as phenol, certain alkaloids, etc., as a rule lost their toxicity as a result of the introduction of the sulphonic acid radical and at the same time lost their neurotropic character.

Ehrlich [2] was thus able to demonstrate for the dyestuffs the manner in which their affinity, and thus their power of penetrating into the nervous cells, was altered by certain changes in their constitution, and to show that, as a result, their distribution in the tissues was a factor having an important bearing upon the relationship between chemical constitution and pharmacological action.

The ready solubility of the narcotics in fatty substances consequently determines the manner in which they are distributed in the various organs and cells. This solubility in fats is also a prime requisite for the absorption of foreign substances by all cells. *Overton* has proved, for the majority of organic substances, that the greater their solubility in fat, as compared with their solubility in water, the more rapidly do they penetrate into the protoplasm. He, consequently, assumed that the protoplasmic membrane is impregnated with certain substances, the lipoids, which possess solution affinities similar to those of the fats.

In addition to a solubility in fat, a certain solubility in water is also essential if a substance is to be absorbed. Substances which are

entirely insoluble in water and which are also not volatile are either split up in order that they may be absorbed, as is the case with the fats, or, like paraffin, they are not absorbed.

Distribution of Narcotics in the Organism.—The distribution of a substance throughout the body is, therefore, determined not only by its solubility in fats, but by its relative solubility in fat and in aqueous media. That, as a matter of fact, the narcotics, when distributed about in the body, are absorbed to the greatest extent by those cells and organs in which fat-like substances preponderate, is shown by the following facts: Chloroform is present in larger quantities in the red blood-cells than in the serum, because lecithin and cholesterin, chloroform-soluble constituents of the erythrocytes, absorb it in relatively larger quantities (*Pohl*). Ether, chloral hydrate, and acetone are distributed in the same unequal fashion between the blood-cells and the plasma (*Frantz, Archangelsky*). The distribution of these various substances in the different organs of the body follows the same law of distribution. The accompanying table gives the results of *Nicloux's* investigation of the distribution of chloroform.

Distribution of Chloroform in Anæsthetized Dogs (Nicloux).

	Duration of anæsthesia			
	30 min.	30 min.	84 min.	80 min.
	Per cent.	Per cent.	Per cent.	Per cent.
Arterial blood	....	0.070	0.064	....
Venous blood	0.0525	....	....	0.049
Cerebrum	0.059	0.0555	0.0545	0.046
Medulla	....	0.085	0.0795	0.075
Cord	....	0.083	0.0805	....
Liver	0.047	0.0505	0.0525	0.0485
Kidney	0.0465	0.0465	0.046	0.039
Spleen	0.0335	0.038	0.031	0.031
Heart	....	0.041	0.0395	0.039
Muscle	0.015	0.0215	0.0245	....
Subcutaneous fat	0.049	....	0.037	0.265
Omental fat	....	....	0.068	0.0685
Perirenal fat	....	....	0.132	0.0875

From this table it is apparent that certain portions of the nervous system, as well as those deposits of fat which are well supplied with blood, contain larger amounts of chloroform than do the other organs.

Fatty tissues are thus seen to compete especially with the nervous system in respect to the absorption of chloroform, and, as a matter of fact, *Mansfeld*[1] has recently shown that certain internally administered narcotics act more powerfully in emaciated than in well-nourished animals, and that their brains contain almost twice as large a portion of the chloral hydrate administered as do those of well-nourished animals, in which the fatty tissues absorb a portion of the narcotic. Such combinations between these narcotics and this tissue (the

fat), as also their combination with other pharmacologically less susceptible tissues,—*e.g.*, the liver,—do not produce readily appreciable results, for the narcosis of the liver-cells or of the red blood-cells does not at once express itself by any change in function, and an acute injury of these less susceptible cells will evidently be produced only by a concentration which would already have caused death by its actions on the nervous system. [Such effects are probably produced not infrequently during anæsthesia. The destruction of the red cells almost certainly occurs in varying degrees under varying clinical conditions, and acute degeneration of the liver, which not infrequently has followed chloroform anæsthesia, would appear to be a late expression of such action.—Tr.]

Solubility Reactions with the Lipoids.—Certain observations on the absorption of dyes by vegetable cells (*Pfeffer*) and by colloidal substances, such as gelatin plates (*Hofmeister*), furnish some data which help us in understanding or imagining the fashion in which the *"solution affinity" of the narcotics for the lipoids determines the proportions in which they accumulate in the different tissue cells.* These dyestuffs pass from dilute aqueous solutions and accumulate in vegetable cells or gelatin plates in much greater concentration, forming firm physical combinations or solutions with the colloidal contents of these cells or plates if they possess a solution affinity for them,—that is to say, if they are more soluble in these colloids than in water (*Spiro*). Under such conditions one may observe an elective absorption, some dyestuffs being rejected and the others continuing to be absorbed until a condition of equilibrium has been established, which corresponds to a certain distribution coefficient between the colloid and water. If now the colored vegetable cells or gelatin plates are transferred to water containing no dye, the dyestuff gradually passes back again into the water. *The process is thus a reversible one.* The absorption of the narcotics by the lipoids of the nervous system which occurs during the narcosis, and the restoration of function after the narcotics have been eliminated from the blood may be considered to take place in a similar fashion, the whole process corresponding entirely with the chemical extraction by agitation of a substance which is soluble in different degrees in two media which are not miscible with each other.

Narcosis the Result of this "Solution Reaction."—From the above discussion, it is apparent that the distribution of the narcotics in the body and their elective accumulation in the nervous system are dependent on their *"solution affinity"* to the lipoids. The theory of narcosis, however, does not stop here, but goes one step farther and endeavors to explain the action of the narcotics as due to this solution reaction. According to this theory, the absorption of the narcotics is not merely a preliminary condition necessary for the occurrence of some still unknown reactions between the narcotics and other constituents of the cells, but *this "solution reaction" with the lipoids of the nerves is the essential cause of the narcotic action.* This conclusion has been reached as a result of determining the quantitative

relationship between the degree of activity of the narcotics and their distribution coefficient between water and fats.

It is naturally impossible actually to determine these distribution coefficients between the lipoids of the brain and the blood-plasma which, according to the theory, will determine the degree of the narcotic power. Consequently, we must be satisfied with an approximate expression of the solution affinity of the narcotics for the lipoids of the nervous system on the one hand and the aqueous body fluids on the other. The distribution coefficient between oil and water may be considered as such an approximate expression, and *Hans Meyer*[1] and *Overton* have determined these coefficients for a very large number of otherwise indifferent narcotic substances, and have compared them with the narcotic power of the different substances, which is expressed by the smallest molecular concentration sufficient to narcotize small tadpoles or fishes swimming in the solutions. The threshold value for the appearance of the narcosis may be quite exactly determined by this method, because a constant condition of equilibrium is established between the solution containing a certain amount of the drug and the animals swimming about in it. For example, in a solution containing one and one-half per cent. of ethyl alcohol, tadpoles are completely narcotized in 2–3 minutes, and a narcosis of constant degree is maintained for hours. In a 1 per cent. solution, on the other hand, no complete narcosis results, even when they remain therein for days.

The comparison of the distribution coefficient with the degree of the narcotic action of the different substances shows that the molecular concentration sufficient to produce narcosis diminishes with almost complete regularity as the coefficient of distribution increases. The narcotic power thus increases with the relative solubility in fat as compared with the solubility in water, as is shown by the accompanying examples:

	Distribution coefficient. $\frac{\text{Solubility in fat}}{\text{Solubility in water}}$	Effective molecular concentration
Trional	4.4	0.0013
Tetronal	4.0	0.0018
Suphonal	1.1	0.006
Bromal hydrate	0.7	0.002
Chloral hydrate	0.22	0.025
Ethylurethane	0.14	0.025
Alcohol	0.03	0.5

A further proof that the narcotic powers of these drugs stand in a regular relationship to their distribution coefficients has been furnished by a series of experiments in which a comparison was made of the narcotic power of certain substances at different temperatures,

certain drugs being used whose coefficients of distribution between oil and water were distinctly altered by the changes of temperature (*Hans Meyer*[2]).

	Threshold of narcotic action, effective dilution of the normal solutions		Partition coefficient $\frac{\text{Solubility in fat}}{\text{Solubility in water}}$	
	At 3° C.	At 30° C.	At 3° C.	At 30° C.
Salicylamide	1 : 1300	1 : 600	2.23	1.40
Benzamide	1 : 500	1 : 200	0.67	0.43
Monacetin	1 : 90	1 : 70	0.093	0.066
Ethyl alcohol	1 : 3	1 : 7	0.024	0.046
Chloral hydrate	1 : 50	1 : 250	0.053	0.236
Acetone	1 : 3	1 : 7	0.140	0.195

With three of these substances the distribution coefficient is increased by heating from 3° to 30°, while with three others the opposite effect is produced. Entirely in accordance with this increase or diminution in the relative solubility in fat, the narcotic power of the substances rises or falls, so that, for example, tadpoles at 30° C. are just narcotized by a certain concentration of chloral hydrate, but wake up again when the solution is cooled and are again narcotized when the solution is again warmed.

By these investigations proof has been furnished for the causal relationship between the narcotic action of certain indifferent lipoid-soluble substances and the power of the nervous system to attract and retain them. However, there are still differences of opinion as to the significance of these relationships. There are those who have been willing to see in the cell lipoids of the nervous system only the solvent which brings the narcotics into contact with the functioning nucleus of the susceptible cells, where they are able to react with other constituents of the cells which are still entirely unknown to us. According to this conception, assumed that this attraction and retention are essential preliminary conditions for the pharmacological action, and that, for example, increasing temperature, by altering the solution affinity, will be accompanied by a similar change in the degree of the pharmacological action. However, the very extensive quantitative parallelism between the pharmacological power of the different narcotics and their coefficients of distribution is not sufficiently explained by this assumption, for if the contact action, which cannot be followed further, is assumed to take place between the narcotics which have penetrated into the interior of the cells and an unknown substance or mixture of substances, one would be forced to conclude that the strength of this contact action is necessarily quantitatively alike with the different narcotics, otherwise the paral-

lelism between the narcotic power and the concentration in the cell lipoids could not be maintained. If one, however, assumes that the narcotics and some unknown constituents of the nerve-cells—for example, the proteids—enter into a physical-chemical reaction, on the degree of which the narcotic activity must depend, this hypothetical reaction would necessarily follow the same scale of chemical relationship as do their soluble affinities to fats. In other words, these hypothetical cell constituents must also possess lipoid properties; otherwise the narcotic power could not remain parallel with the distribution coefficients of solubility in fats. Consequently, we see in the lipoids of the nerve-cells not merely substances which act as the means of bringing about a solution of the narcotics in the cells, but we see in them the actual substance or substances which are acted upon by the narcotics. As a result of their loose physical-chemical combination with the narcotics, these lipoids lose their normal relationship to the other cell constituents, and as a result the entire chemism of the cell is inhibited.

Among the results of this inhibition is a diminished absorption or utilization of oxygen, which has been shown by *Verworn* and his collaborators to occur in narcosis. This deprivation of oxygen by itself produces a depressing or paralytic effect very much in the same way as does narcosis (*Mansfeld*[2,3]). The inhibition of oxidation is, therefore, certainly a factor accompanying chloroform or ether anæsthesia which tends to augment the narcosis, but, just as certainly, it is not the cause of the anæsthesia, for vital phenomena, such as nervous excitation, are inhibited only by many times greater degrees of narcosis than are necessary to cause an inhibition of the consumption of oxygen (*Dontas, Höber, Warburg*[1,2]), and, furthermore, narcosis inhibits those very phenomena of life for which energy is not furnished by oxygen (*Winterstein*).

There has been a wide-spread tendency to assume that the proteids alone are essential factors in the functional activity of cells, but the general occurrence of lecithine and other lipoids in all living cells speaks against this view. It appears that these substances do not play in the cell a rôle of reserve substances as do the true fats, but that they are combined intimately with proteid to form a portion of the functioning protoplasm. Combinations of lecithin and proteid, however, manifest similar solution affinities to those of lecithin and must, therefore, in their relationship to this narcosis theory, be considered as lipoids.

The fact that the narcotics of this series possess the power of paralyzing not only nervous elements but also all living cells is quite in accord with this general distribution of the lipoids in all cells. That the narcotics are primarily neurotoxic is due to the fact that the disturbance of function which they cause expresses itself most clearly in the nervous organs.

Side Actions of these Drugs.—This theory of narcosis is based on the presumption that further investigations will confirm this parallelism between the anæsthetic power and the partition coefficient of

solubility in the lipoids and the plasma. In no case, however, is an absolute parallelism to be expected, for the partition coefficient between oil and water is only an approximate expression for the actual distribution of the anæsthetics between the cerebral lipoids and the blood-plasma. Above all, it is only with those members of this group which are chemically indifferent and which do not readily enter into chemical reactions that one may assume an absence of affinities for other constituents of the nervous tissues. As a matter of fact, the various side actions of the different narcotics indicate clearly that such side reactions also occur. However this may be, the basic narcotic action of the different members of the alcohol-chloroform group is, in principle, so similar, that we are compelled to assume that it is caused by a reaction which is common to them all. The more, however, the essential pharmacological actions of narcotic substances differ from the typical action of this group, the more necessary is it to assume that other reactions are involved in producing their atypical actions. Thus, for example, phenol, as a lipoid soluble substance, might be considered as belonging to this group, and, as a matter of fact, it does produce some narcotic effects, but, as it possesses strong affinities for proteids and other constituents of the body, it also produces its own peculiar pharmacological effects.

Other Types of Anæsthesia.—This theory cannot by any means be used to explain every kind of anæsthesia, for many other quite different disturbances of the chemical equilibrium of the nerve-cells must inhibit their functions and produce superficially similar symptoms, as is, for example, the case with the salts of magnesia (*Meltzer*[1,2]). The method of action described above applies, therefore, only to chemically relatively indifferent substances.

In this sense, substances such as *free* CO_2 and NO_2 which chemically do not even remotely resemble the members of the aliphatic series, may also be considered as belonging pharmacologically to the group of alcohol, for they act as narcotics and are soluble in the lipoids, while the carbonates, which do not produce such effects, are also insoluble in the lipoids. On the other hand, it is in the highest degree probable that besides being soluble in the lipoids the alkaloids possess other affinities for other cellular constituents, for the manifold character of their pharmacological actions of itself indicates that they must act on different constituents of the nerve-cells. The alkaloidal drugs do not exhibit such a uniform type of pharmacological action as do the members of the alcohol group, as is shown by the fact that not all types of cells are pharmacologically influenced by them, numerous vegetable cells, for example, being entirely unaffected, a fact which by itself renders it improbable that their fundamental action is due to their affinity to the lipoid substances, which are such universal constituents of cells.

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OTHER CENTRAL DEPRESSANTS

In this chapter mention has been made only of the therapeutically most important of the many organic drugs which exert pharmacological actions on the central nervous system. Such actions of numerous other drugs will be described in connection with the discussion of their other more important actions on other organs. Other drugs, again, which act primarily and chiefly on the central nervous system possess only a toxicological significance, although among them are some which formerly were widely used in medicine, but which are to-day used so seldom that they may be dismissed with a few words.

ACONITE, the root of Aconitum napellus, or monkshood, is such a drug, which is official and is still quite extensively used, particularly by the homœopaths.*

The various aconitines on the market differ quite markedly from one another, but are all esters of various aconines with acetic, benzoic, and other acids. Locally applied, they cause a primary stimulation followed by a later depression of the sensory nerve-endings, causing first a feeling of warmth and tingling and later anæsthesia. Repeated administration of doses of 1–2 mg. causes paræsthesia, formication, and numbness of the extremities, with diminution or complete abolition of sensations of pain, such as those of neuralgia. These

systemic effects are probably the result of their action on the central nervous system or on the spinal ganglia (*Wartmann, Cohn*). Toxic doses are followed by convulsions, due to asphyxia, and by paralysis and death. Even very small doses, mere fractions of a milligram, may cause serious symptoms, and 3–4 mg. of aconitine nitrate may cause death. The cases of poisoning which have been reported have usually been due to the variable strength of the different aconitine preparations (*Kunkel, Kornalewski*).

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Numerous inorganic substances also exert toxic actions on the central nervous system, and even those salts which are normal constituents of the body may produce these effects if, as a result of their intravenous or subcutaneous administration in too large quantities, the normal equilibrium of the different ions is disturbed.

Magnesium salts occupy a peculiar position among the salts, causing, without any primary stimulation, an elective paralysis of the central nervous system, the heart being hardly at all affected by them and the muscles retaining their excitability (*Meltzer* and *Auer*[1]). It appears that Mg ions, which in relatively small amounts are normal constituents of the tissues, when present in sufficient concentrations abolish the excitability of all nervous organs. In the frog a curare-like paralysis of the motor nerve-endings is the most striking effect produced (*Binet*). This effect is produced also in warm-blooded animals, but, as it occurs later than does the stoppage of the respiration, it can be observed only if artificial respiration be carried on (*Wiki*). This effect on the respiration is preceded by complete anæsthesia, paralysis of the higher motor centres, and depression of the blood-pressure (*Meltzer* and *Auer*[2]). The vagus nerve-endings also lose their excitability, and the motor and sensory nerve-trunks, if brought in direct contact with magnesium salts, lose their conductivity. Quite recently these actions have been utilized in practice (*Meltzer*) [but, with the exception of the local anæsthetic actions, apparently with little success. Injected intradurally, solutions of magnesium salts cause a spinal analgesia resembling that produced by cocaine, but more lasting. Practical experience with this method has, however, shown that it is attended by such danger that it has been abandoned, at any rate for the present.—Tr.].

All the toxic symptoms produced by magnesium salts may be caused to disappear promptly by the intravenous injection of calcium salts (*Meltzer* and *Auer*[3]), calcium ions appearing to act antagonistically to those of magnesium and to be able to restore the equilibrium between the various ions when it has been disturbed by an excess of Mg ions.

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Potassium salts do not cause such a well-developed elective paralysis, but when administered intravenously or subcutaneously they exert toxic actions both on the nervous system and on the heart. [It is in the highest degree improbable that the medicinal administration of potassium salts ever produces such a "potassium" toxic action. The common belief that potassium salts are "too depressing" is based only on a misinterpretation of experimental evidence.—Tr.]

THE BROMIDES

The anions of neutral salts, particularly Br ions, may also exert specific therapeutically useful actions on the nervous system. As these salts in their pharmacological actions show a certain resemblance to the hypnotics, it is appropriate to take up their discussion at this time. In the body the bromides of the different alkaloids produce entirely similar pharmacological effects, and consequently their pharmacological actions must be attributed to their bromine component and not to their different metallic components (K, Na, etc.).

Soon after *Ballard* in 1826 discovered bromine and the bromides, KBr was employed in therapeutics, at first as a substitute for KI, which chemically so closely resembles it. Very soon its uselessness in lues was recognized, but at the same time its efficiency as a sedative for the central nervous system became apparent. In 1864 it was first used by *Behrend* in certain forms of sleeplessness, and a little later by *Vigouroux* and *Voisin* in epilepsy.

Action of Large Doses in Health.—Concentrated solutions of the bromides irritate the tissues chiefly as a result of their salt action, but dilute solutions produce no marked irritation and are rapidly absorbed. In man very large doses (10 gm.), in addition to causing a salty after-taste in the mouth and a feeling of pressure and warmth in the epigastrium, cause a certain amount of stupor, with disturbance of the powers of perception as well as of the speech. Besides this, such doses cause a very complete abolition of the reflex irritability of the palate and posterior pharyngeal wall, so that gagging does not follow mechanical irritation (*Kross*). The bromides are not to be considered true hypnotics, for in man therapeutic doses of 1–2 gm. do not produce a condition resembling normal sleepiness and fatigue. It is in accord with this that in experiments on animals no narcosis results from the administration of the bromides, but only a diminution of the central reflex excitability when large doses are given. However, in states of nervous excitement and in epilepsy their administration produces a quieting or sedative effect.

Thus far we have no knowledge of the details of the manner in which these effects are produced. Psycho-physical analysis has shown only that the bromide salts influence those psychic processes which may be experimentally measured, in a very different fashion from the true hypnotics, for doses of 2–4 gm. neither impair the perception of sensory stimuli nor the inauguration of motor acts (*Löwald*). On the contrary, intellectual work is favorably influenced by the bromides, particularly if the performance of such work has been rendered difficult as the result of pronounced feelings of discomfort. It, therefore, appears that under such circumstances bromides eliminate certain central excitations, which accompany feelings of discomfort and which interfere with the performance of mental work.

In conditions of disease also, the bromides act favorably upon such conditions of nervous hyperexcitability as are accompanied by discomfort or malaise, as is often the case in neurasthenia and epilepsy. Bromides also often produce sedative and hypnotic effects in conditions of hyperexcitability in arteriosclerotic patients (*Homburger*), but, on the other hand, they are ineffectual in such conditions as simple maniacal excitement (*Löwald*). It, therefore, appears that, when potassium bromide is administered in the usual hypnotic and sedative doses of 1–2 gm., its effects are due to a very specific action on the cerebral cortex.

Action in Epilepsy.—The diminution of the reflex excitability of the central nervous system, which may be demonstrated experimentally after large doses of bromides, appears to be of significance in connection with the use of KBr in the treatment of epilepsy, in which it is administered in daily dosage of 5–10 gm. or more, amounts which even in normal individuals exert a distinct influence on the cerebral sensory and motor functions.

In experiments on animals, *Albertoni* has shown that large but nontoxic doses of KBr, especially when administered repeatedly, markedly lessen the electric excitability of the cerebral motor centres. While in the normal controls stimulation of the cortex with electric currents of a certain strength always caused general epileptiform convulsions, showing that the stimuli spread from the directly stimulated centres over the whole motor region, in the bromidized animals no generalized convulsions occurred, but only clonic movements of the muscles whose motor centres lie close to the stimulated points. This is best explained on the assumption that the drug *blocks or renders difficult the passage of impulses along the paths which connect the various motor centres.* While there can be no question of the favorable influence exerted by the bromides on the number and intensity of the epileptic attacks, we cannot obtain any closer insight into the manner in which they do so until the cause of epilepsy is more completely understood.

Retention in the Body.—The favorable therapeutic effects of the bromides do not become manifest until a rather high degree of satura-

tion of the organism has been produced, and when this occurs the effect in diminishing the epileptic attacks persists for some time after cessation of medication. This is due to the fact that bromides are not completely eliminated in the 24–36 hours following their ingestion, but that, in spite of the fact that their elimination starts almost immediately, only from one-tenth to one-fourth of the amount administered is excreted in the first 24–36 hours, and that even 20 days after cessation of its administration it has not been completely eliminated (*Féré, Hebert et Peyrot, Nencki, Pflaumer*). It is thus evident that the organism retains large amounts of bromides for a considerable period (*v. Wyss*,[1,2] *E. Frey*).

As a result of this retention when bromides are regularly ingested, a certain SATURATION OF THE ORGANISM results. While at the start from 10 to 48 per cent. of the daily dose is eliminated, the amount varying with the amount of urine excreted, the percentage eliminated increases from day to day, so that when, for example, 7 to 8 gm. of NaBr are taken daily for two weeks or so, a state of bromine equilibrium results, in which the elimination and absorption of bromine are equal (*Laudenheimer, v. Wyss*,[1,2] *Fessel*).

When bromides are taken regularly, the blood always contains bromides, and the chlorides are correspondingly diminished, so that when saturation has been produced ¼ to ⅓ of the Cl of the blood-serum has been replaced by Br (*Laudenheimer, v. Wyss*,[1,2] *Ellinger*). The bromides also partially replace the chlorides in other tissues, accumulating in the largest amount in those organs which normally are richest in chlorine, in which they to a certain extent assume the rôle of chlorides. For instance, HBr appears in the gastric juice (*Külz, Nencki*). According to *Hoppe,* the percentage of HBr in the gastric juice may serve to indicate the degree of bromine saturation which has been attained.

If this replacement of chlorides by bromides occurs to too great a degree, toxic symptoms appear, in which case the free administration of common salt is curative (*v. Wyss*[1, 2]), as it accelerates the elimination of the bromides and replaces the bromides in the tissues and body fluids (*Laudenheimer, Ellinger*).

It is of practical importance to remember that the accumulation of bromide in the body is influenced by the amount of NaCl ingested, for the curative effects in epilepsy are obtained more rapidly and with smaller doses if the diet be one poor in salt (*Richet*). Bromism, too, occurs more rapidly with such diet.

The following figures, from *Ellinger* and *Kotake,* show how in rabbits the elimination of bromides is augmented by the simultaneous administration of NaCl and not by that of the other salts, and also show how the blood contains larger amounts of bromides when the diet is poor in NaCl than when this salt is administered freely.

NaBr–NaCl Experiment.	NaBr–Na Acetate Experiment.
Constant diet—0.322 gm. NaBr and 2.0 gm. NaCl daily for 6 days	Same diet and 0.322 gm. NaBr and 2.0 gm. sodium acetate for 6 days
Total Br excreted	
0.74 gm.	0.41 gm.
Blood on 6th day contains	
0.064 per cent. Br = 9.52 per cent. of the total halogen mols.	0.16 per cent. Br = 23.8 per cent.

A comparison of the following two experiments shows very strikingly how the bromine saturation when once attained is rapidly lessened by the administration of NaCl and how this salt, in contrast to other salts, accelerates the elimination of Br in the urine.

Period I.

Rabbit A:	*Rabbit B:*
For 8 days 0.322 gm. NaBr daily and no NaCl.	For 8 days 0.322 gm. NaBr daily and no sodium acetate.
Urine on 7th and 8th days contains	
Cl 0.67 gm.; Br 0.28 gm. = 15.3 per cent. of the total halogen mols.	Cl 0.56 gm.; Br 0.26 gm. = 16.8 per cent. of the total halogen mols.
Blood on the 8th day contains	
Cl 0.22 per cent.; Br 0.15 per cent. = 23.8 per cent. of the total halogen mols.	Cl 0.23 per cent.; Br 0.16 per cent. = 23.8 per cent. of the total halogen mols.

Period II.

For four days 0.322 gm. NaBr + 2.0 gm. NaCl daily	For four days 0.322 gm. NaBr + 2.0 gm. sodium acetate daily
Urine on 1st and 2d days contains	
Cl 2.52 gm.; Br 0.51 gm. = 7.7 per cent. of the total halogen mols.	Cl. 0.67 gm.; Br 0.26 gm. = 15.3 per cent. of the total halogen mols.
Blood on the 4th day contains	
Cl 0.28 per cent.; Br 0.064 per cent. = 9.2 per cent. of the total halogen mols.	Cl 0.24 per cent.; Br 0.18 per cent. = 23.9 per cent. of the total halogen mols.

Bromism.—The accumulation in the body of excessive amounts of bromides would appear to explain the undesirable bromide actions which at times are observed. In milder cases these affect chiefly the skin and mucous membranes, causing various exanthematous eruptions, usually an acne, but in severer cases causing pustular eruptions. Coryza, conjunctivitis, and catarrhal inflammations of the respiratory tract also occur. These lesions are probably all due to irritation caused by the bromides or their transformation products during their excretion by the glands of the skin and mucous membranes, where, probably under the influence of acid secretions, hydrobromic acid is formed, which is readily decomposed, liberating free bromine. As bromine is a powerful irritant to the tissues, it is easy to understand how the local lesions are produced. It is probable that the gastro-intestinal disturbances, which are often observed in cases of chronic bromism and

which cause emaciation and cachexia, are dependent on the excretion of the bromides through the alimentary mucosa. Disturbances of the central nervous system, leading to loss of memory and apathy and to motor and sensory disturbances, may also be observed. NaCl may be used as an antidote in such conditions.*

Preparations.—For therapeutic purposes the bromides of the alkalies are the preparations most used. Those most commonly used are potassium bromide (67 per cent. Br), sodium bromide (77 per cent. Br), and ammonium bromide (81 per cent. Br), which are all colorless crystalline powders very soluble in water, and with a salty, rather disagreeable taste. With the two first named no qualitative or quantitive differences are observed in their pharmacological action, except that the sodium salt is slightly more powerful on account of its larger bromine content. With large doses of ammonium bromide the local and systemic actions of its basic component are evident. In order to avoid gastric irritation, these salts should be administered well diluted with water.

With the idea of avoiding the undesirable effects of the bromides a number of organic bromine compounds have recently been introduced, for which various advantages have been claimed. In judging of these claims it must not be forgotten that these organic compounds contain much smaller quantities of bromine than the inorganic bromides, which probably explains their slighter toxic power [and also their slighter therapeutic efficiency.—Tr.] Among these may be mentioned: Bromipin, brominized sesame oil, obtainable in two strengths, 10 per cent. and 33⅓ per cent. Br; sabromin, dibrombehenate of calcium, containing 29 per cent. Br; and bromine compounds with albumin, such as bromeigone (11 per cent. Br), or with gelatin, such as bromocoll (about 20 per cent. Br). Up to the present neither clinical experience nor experimental evidence has demonstrated that these preparations possess any real superiority to the bromide salts (*Bilinski, Bermann*).

Valerian is another drug producing mild hypnotic effects, which, although no longer so highly esteemed as formerly, is still often used in hysterical patients. As the active constituents of the drug are very unstable, its galenic preparations are of uncertain and variable potency.

The active constituents which are present in the oil of valerian exert some narcotic action on the cord and the higher cerebral centres (*Binz, Grisar*). From it there have been isolated borneol and the bornyl esters of different fatty acids, particularly isovalerianic acid, which esters, like the crude drug, exert a distinct depressing action on the central nervous system (*Kionka*). Borneol isovalerate under the name of bornyval, and a mixture of menthol with the menthyl ester of valerianic acid under the name of validol, have been introduced as substitutes for the crude drug or its galenic preparations, but they too are unstable and, like isovalerianic acid itself, are likely to prove inactive (*Kochmann*). Perhaps valvyl, valerianic acid diethylamide, is the best of these substitutes for the crude drug. It appears to act as a mild hypnotic and sedative.

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CHAPTER III

PHARMACOLOGY OF THE SENSORY NERVE-ENDINGS

The end-organs of the sensory nerves are everywhere exposed to the pharmacological action of chemical substances.

Stimulation of the sensory nerves expresses itself as pain, as a feeling of heat or cold, etc., which often excite reflexes, as, for example, when stimulation of the sensory nerves of the stomach causes vomiting or when irritation of the trigeminal terminations in the nasal mucous membrane produces sneezing. With the corrosives, the stimulation of the sensory nerve-endings is only a symptom of the general action on all tissues which results in the death of the cells. There are, however, certain substances, such as veratrine, which exert an absolutely specific action on these organs.

Reflex Effects of Sensory Stimulation.—In collapse and in narcotic poisoning, agents stimulating these organs are frequently employed to produce a reflex stimulation of the depressed respiratory and circulatory centres. For such purposes mechanical (friction, slapping, etc.), thermic, or chemical irritation of the skin may be employed. As chemical irritants or stimulants only such agents may be used as penetrate the horny epidermis with sufficient rapidity to reach the sensory end-organs, volatile substances, such as mustard oil or acetic ether, being best adapted for such purpose. Reflexes from sensory irritation without doubt play an important rôle in producing the effects caused by the subcutaneous injection of camphor and of ether, especially in the latter case. Olfactory stimulation, as by ammonia, and stimulation of the taste, as by the ethers of wines with strong bouquet, are other examples of sensory stimulations, which reflexly affect the respiration and circulation.

LOCAL ANÆSTHESIA

This depends on the feasibility of temporarily depressing the excitability of sensory nerve-endings without permanently damaging them, and in recent years its field of usefulness has been steadily widened.

Local anæsthesia may be induced by suppressing the excitability of the sensory nerve-endings, "terminal anæsthesia," or by preventing the conduction of nervous impulses in the nerve-trunks, "nerve blocking." The blocking of the centripetal sensory fibres may occur at any point between the point at which the posterior roots enter the cord and the terminal end-organs. When it is the more delicate terminal nerve-fibres which are affected, it is difficult to distinguish the effects of such action and those resulting from depression of the

terminations of the nerves. [As a matter of fact, both the terminal organs and the terminal fibres are usually affected together.—Tr.]

Anæsthetization of the sensory organs may be produced by either physical or chemical action. Interruption of sensory conductivity by COMPRESSION is the oldest known method of causing anæsthesia. The "going to sleep" of the extremities, with the resulting paræsthesia and numbness, which is caused by accidental compression of nerve-trunks against bone, is a common experience, and is an illustration of anæsthesia by compression. In former times surgeons frequently induced anæsthesia by tightly ligaturing an extremity. [Infiltration anæsthesia (see below) depends wholly or in part on the effects of compression of the sensory terminal fibres and organs.—Tr.] Neuralgic pain may often be alleviated temporarily by pressure on the trunk of the nerve affected.

Anæsthesia may also be induced by producing a LOCAL ANÆMIA. An example of this is the anæsthesia which soon follows the ligation of a large vessel, such as the crural artery, the terminal sensory organs being the first structures affected, while the nerve-trunks retain their excitability for a long time, even after complete interruption of the blood supply. Anæmia alone, however, does not induce anæsthesia quickly enough for practical purposes, but the application of the Esmarch bandage favors local anæsthesia by causing both compression and anæmia. As will be seen later, both compression and anæmia, induced in various ways, are of much value in augmenting and aiding the action of cocaine and similarly acting drugs.

LOCAL ANÆSTHESIA BY COLD.—Extreme cold can also render unexcitable both the terminations and the trunks of the sensory nerves, as is evidenced by the well-known fact that the extremities become insensitive when exposed to ice and snow.

James Arnott, in 1849, was the first to make a systematic use of cold for the induction of local anæsthesia. His method consisted in applying a mixture of ice and salt to the skin of the part to be anæsthetized. *Richet*, in 1859, employed the cold resulting from the evaporation of ether for the purpose of anæsthetizing the skin, and *Richardson*, in 1866, improved the technic by introducing the ether spray.

The lower the boiling point of the evaporating fluid the more intense is the cooling of the skin, and, therefore, ETHYL CHLORIDE, which boils at 12.5° C., freezes the skin much more rapidly, and for this purpose has almost completely superseded ether. Mixtures of ethyl chloride with the gaseous METHYL CHLORIDE, which boil at 2–0° C., have been introduced and appear to have advantages as means of rapidly freezing tissues. "Anæsthyl Bengue" and " metæthyl Henning " are two such preparations.

When exposed to low temperatures, the smooth muscles and the vessels of the skin first contract and the skin becomes pale, but on longer exposure reddens. If the temperature be reduced far enough

to freeze the skin, it suddenly becomes white and hard, the blood flow ceases, and the sensory nerves lose their excitability, so that the tissues become insensitive. The anæsthesia is the combined result of the cold and the anæmia. Too long continuation of the freezing may result in gangrene. At the start, too rapid freezing causes quite sharp pain, but gradual freezing and thawing are painless. The pain preceding the anæsthesia is therefore less with the ether spray than when ethyl chloride is used. [With reasonable care freezing with ethyl chloride is practically painless.—Tr.]

A thorough freezing with complete anæsthesia is attainable only in the skin, for the penetration of the effects of cold is limited in tissues freely supplied with blood. Consequently, the more hyperæmic mucous membranes may be from inflammation, the more incomplete is the anæsthesia from cold. In spite of these drawbacks, freezing of the surface often renders good service when small incisions are to be made or an abscess opened. Especially is this the case in dental practice.

LOCAL ANÆSTHESIA BY CHEMICAL AGENTS

Until *Koller,* in 1884, made known the anæsthetic action of cocaine, local anæsthesia was induced only by the methods mentioned above, and practically the only method used was that based on freezing. The possibility of electively influencing the sensory nerves by chemical substances was for the first time demonstrated by the action of cocaine. [Aconite and other drugs, however, had long been used to produce relative local anæsthesia.—Tr.]

Any substance, which reacts chemically with the constituents of a sensory cell, necessarily causes a change in the constitution of its protoplasm and affects its function in some degree and manner. Therefore all substances, which, as a part of their general destructive action on the tissues, possess strong chemical affinities for the constituents of protoplasm, cause at first violent stimulation of the sensory elements, or pain, and later insensibility or permanent destruction of their function. Consequently, true corrosives cannot be utilized to induce anæsthesia. As, however, the sensory end-organs are especially susceptible, they are affected by very weak concentrations of the general cell poisons,—*e.g.,* by agents precipitating proteids. In this manner certain CORROSIVES in relatively great dilution may induce local anæsthesia without necessarily harming other tissue elements. CARBOLIC ACID is such a substance, which readily penetrates the skin, in proper dilutions causing first burning and later insensibility. Dressings saturated with 1–2 per cent. carbolic acid solutions, when left in contact with the skin, produce a local anæsthesia, *but they may also cause gangrene.*

A large majority of the substances which react to any degree with the protoplasm of the peripheral sensory nervous elements paralyze or anæsthetize these only after first causing irritation and pain. A

typical example of such substances is ammonia, which, although it specifically paralyzes motor nerve-endings (*Grützner*), first stimulates exposed sensory nervous elements and afterwards produces a marked anæsthetic effect (*Gradenwitz*). Such substances which cause first local pain and later local anæsthesia are very numerous, and have been named by *Liebreich* "ANÆSTHETICA DOLOROSA."

INFILTRATION ANÆSTHESIA

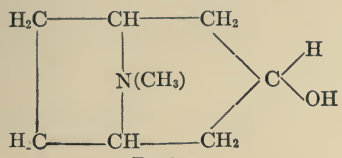
The Effects of Anisotonic Solutions.—On account of its rich supply of sensory terminal organs, the human skin is the tissue most suitable for testing the effects of this procedure (*Heinze, Braun* [1]). Solutions at the temperature of the body are injected into the skin, causing pale wheals to rise above the surrounding skin (*Schleich*). When thus applied, distilled water causes first pain and later insensibility, which may last for a quarter of an hour. Addition of salt lessens both the primary pain and the anæsthesia, while 0.9 per cent. NaCl solutions, which are isotonic with the tissues, can be injected without causing pain, but as the concentration is increased above 0.9 per cent. the primary pain and the later anæsthesia increase progressively. These effects are due either to the swelling up of, or the abstraction of water from, the tissue cells, which is caused by the hypotonic or hypertonic solution, the former giving off water to and swelling up the cells, the latter abstracting it from the cells and causing them to shrivel up or shrink. These effects of such solutions, which can be closely followed in vegetable cells, in the erythrocytes, and in other readily isolated cells, also occur in the nerve-cells. *Braun's* [1,2] observations—that the "indifferent point," where the least effect was produced, was found, with solutions of very different substances, always to coincide with concentrations isotonic with the blood—indicate clearly that, quite aside from the chemical effects of different salts, acids, bases, and organic substances, the physical influence of inhibition or of abstraction of water can affect the function of the sensory cells. This fact is of importance in connection with all injections into the tissues, and for this reason *Braun* insists on the use of osmotically indifferent solutions when inducing infiltration anæsthesia by *Schleich's* method. Only in this way may the pain due to the swelling or shrinking of the nerve-cells be avoided and the pure cocaine effects be obtained. [In infiltration anæsthesia, pressure also plays some rôle.—TR.]

COCAINE

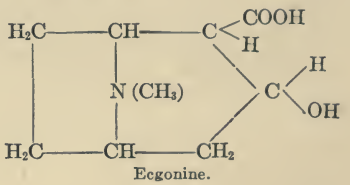
In contrast to the large number of substances belonging to the group of the " anæsthetica dolorosa " is the relatively small number of substances which exert an elective action on the peripheral sensory elements, and which possess the power of causing a paralysis without any marked stimulation of these elements. Cocaine was the first drug known to possess such action, but since its introduction a number of

drugs have been discovered or synthetized which produce similar effects and resemble it more or less closely in their chemical structure.

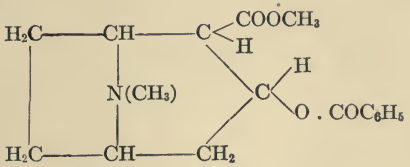
Cocaine, first prepared in 1860 by *Wöhler* and his pupils, occurs in the coca leaves in the proportion of about ½ per cent. From the rather insoluble, readily crystallized alkaloid, soluble salts may be prepared, of which the hydrochlorate alone is used. It is an ester of complex structure, resembling atropine in its constitution. On boiling with acids or alkalies, it splits up into benzoic acid, methyl alcohol, and the base, ecgonine, which closely resembles tropine, a base which, with tropaic acid, results from the decomposition of atropine. The foundation of both the bases is a double ring, which, it may be assumed, is formed by the combination of a pyrrolidin ring with a piperidine ring. Ecgonine is tropine carbonic acid. The close constitutional relationship between cocaine and atropine is well shown in the accompanying graphic formulæ.



Tropine.



Ecgonine.



Cocaine, benzoylecgonine methyl ester.

Benzoylecgonine has no local anæsthetic action for the typical cocaine actions develop only when this substance is esterfied, as, for example, by methylation. Its ethyl ester and other homologous substances act like cocaine (*Poulsson*). The pharmacological activity of the drug depends also on the presence in the molecule of the benzoyl radical, for, when other acid radicals are substituted, the anæsthetizing action is weakened or destroyed.

Source.—Cocaine is obtained from the leaves of Erythroxylon coca, a plant indigenous in South America, especially in Peru and Bolivia, where it was held to be a sacred object and was valued as an indispensable stimulant (Genussmittel). The leaves mixed with ashes or lime are chewed by the natives, who attribute the most wonderful effects to this practice, claiming that it increases the bodily powers and renders one more eager for work and more cheerful. Especially, however, they believe it to render one more capable of great exertion without fatigue and of resisting hunger and thirst. These effects have been confirmed by the observations of many travellers. Such reports led to repeated investigations of the coca leaves in European lands, but at first only negative results were obtained, as the investigators attempted only to determine whether the coca leaves acted as a means of lessening combustion in individuals who took their usual nourishment.

HISTORICAL.—Therapeutically the most important property of cocaine is its paralytic action on the sensory nerve-endings. Step by step the induction of local anæsthesia by the use of cocaine has been logically developed and has acquired a constantly increasing importance for general surgery, until to-day it represents an extremely valuable supplement to general anæsthesia.

The history of the evolution of the knowledge and use of cocaine is a very interesting example of the slowness with which an important fact may be recognized and of how, after a discovery has been made, a long time may elapse before its true significance is appreciated. *Wöhler*, who was the first to prepare cocaine in pure form, in his description of its properties, wrote of it: "It tastes bitter and affects the nerves of the tongue in a peculiar fashion, so that for a time the place of application is benumbed and almost without feeling." The local anæsthesia from chewing the leaves was also noted long ago (*de Marle* 1862, *Scherzer* 1865), while *Moreno y Mays* in 1868 and *v. Anrep* in 1880 demonstrated the local anæsthetic action in animals, and the latter author demonstrated on himself that, by subcutaneous injection of this drug, the skin could be rendered insensitive to a pin prick. However, it was only after the epoch-making communication of the Viennese oculist, *Köller*, who in 1884 demonstrated its practical value, that ophthalmology, laryngology, and other branches of surgery quickly adopted it.

GENERAL PHARMACOLOGICAL ACTION.—Cocaine is a general protoplasmic poison, which, if absorbed in sufficient amounts, first affects the central nervous system. If, however, it is applied locally to the tissues and brought in contact with nerve-endings and fibres, its first action is that of suppressing the function of the sensory nerve elements.

It is of fundamental importance for the local action of cocaine that, in contrast to most alkaloids, ITS SALTS VERY READILY PENETRATE INTO LIVING CELLS and thus easily spread into the tissues.* On account of the horny nature of its outer coating, human skin is impermeable to cocaine, but all living cells readily absorb it, and thus when applied to the surface of intact mucous membranes it readily reaches the sensory nervous elements. The skin of the frog behaves toward it similarly, on account of its numerous glands and the fact that it is constantly moist and able to give off or take up gases and aqueous solutions. This animal is, therefore, especially adapted for the demonstration of the anæsthetic power of cocaine (*Gradenwitz*).

Local Anæsthetic Action.—In the "spinal" frog (one in which the higher portion of the central nervous system is destroyed) reflexes follow promptly on sensory stimulation of the skin, for example on the application of ⅙ per cent. HCl. If, however, the skin of one leg has been bathed with a solution of cocaine, this leg is withdrawn from the acid much later than the other, and with sufficiently long bathing with cocaine, even the strongest irritation with acid fails to produce a reflex movement, for the local anæsthesia is absolute. This experiment succeeds even better after abolition of the circulation throughout the body, for then there is no danger of absorption of enough cocaine to affect the central

* According to *Gros*, cocaine salts do not themselves penetrate the living cells, but the free base is set free by hydrolytic action and enters the cells. Consequently, the more strongly the salts of the different local anæsthetics are dissociated the more powerfully do their solutions act. *Gros*, therefore, for certain purposes recommends the bicarbonate of novocaine as superior to other salts formed by it with the strongest acids. (See p. 130.)

nervous system. The behavior of the other leg which responds normally to irritation demonstrates that the failure of reflex movements is not due to a paralysis of the cord, and the normal motor reaction of the cocainized leg when the other leg is stimulated proves that the motor nerves are not affected.

Besides those of the algesic nerves the nerve-endings of certain other sensory nerves are paralyzed, as for example those of the nerves for taste, touch, and smell (*Zwardemaker*), while reflexes from the mucous membranes, for example from the conjunctiva, are suppressed by its local application. If ammonia be held under a rabbit's nose, under normal conditions, the respirations cease in the expiratory phase, as a result of a reflex originating in the trigeminal endings in the nasal mucous membrane. As cocainization of the nasal mucous membrane prevents this reflex (*Loewy u. Müller*), it has been suggested that the analogous disturbing reflexes occurring during administration of the general anæsthetics be prevented by a preliminary cocainization of the nasal mucous membrane. For operations on the larynx and in the nose and pharynx, suppression of the reflexes is often of as much importance as is the suppression of the pain sense.

The anæsthetic action of this drug on the nerve-endings and smaller branches is also readily demonstrable in open wounds (*Grützner*). Best of all, however, it can be shown in the skin, by the method mentioned on page 120, where 1 part in 20,000 in 0.9 per cent. NaCl solution destroys the sensibility of the wheals for a considerable time. The duration of the anæsthesia increases with the concentration employed, lasting for 15 minutes with 1 per mille, and for 25 minutes with 1 per cent. solutions (*Braun, Heinze*). The anæsthesia is preceded by pain lasting a short time, only when more concentrated solutions are employed.

Anæsthesia by Nerve Blocking.—Cocaine is able to penetrate through the medullary sheath of nerve-trunks and to suppress their conductivity so that the region innervated is rendered anæsthetic (regional anæsthesia). The thinner the connective-tissue sheaths of the sensory nerves, the more susceptible are they to this blocking. Therefore, the finer terminal nerve-fibrils are scarcely less susceptible to cocaine than are the nerve-endings. As the drug penetrates more slowly into the larger nerve-trunks, a relatively high concentration is necessary for their anæsthetization when the injection is made in their neighborhood (*perineural* injection), but with *endoneural* injection even quite dilute solutions quickly induce anæsthesia.

Elective Action on Sensory Fibres.—Cocaine acts electively on the sensory fibres, for, when a solution is applied to a mixed nerve, the sensory fibres are more affected than the motor (*Alms*).

After 1 minute the conductivity of the sensory fibres of the frog's sciatic is abolished, while for some time longer motor conductivity is unaffected (*Kochs*). *Dixon* has confirmed this in the rabbit, and *Santesson* has shown that contact for 15 to 18 minutes with a 5 per

cent. solution of cocaine so completely abolishes sensory conductivity of the nerves that even the strongest tetanizing stimulus peripherally to the point of cocaine application produces no reflexes, although the motor conductivity remains unaffected for about one hour longer. *It is thus evident that not only the terminal organs of motor and sensory nerves react differently to various drugs,—e.g., to curare and cocaine,—but that the two types of nerve-fibres show a similar difference in their pharmacological reactions.* Another example of such difference is their behavior toward ammonia, which stimulates motor fibres hardly at all but which stimulates sensory fibres more powerfully than either NaOH or KOH (*Grützner*).

Differences in the Pharmacological Reactions of Different Kinds of Nerve-fibres.—It might be possible to explain the difference in the reactions of these two types of fibres by assuming that a different degree of susceptibility to stimulation is a characteristic of their respective terminal organs, as a consequence of which, that minimum stimulation of the sensory fibres which would be sufficient to produce an effect in the central reflex mechanism, would be greater than that necessary to cause an effective stimulus to pass down the motor nerves to their terminal organs. More briefly expressed, we might assume a higher threshold value for stimulation of sensory nerves than for that of motor nerves. However, *Dixon* has shown that cocaine exerts a selective action on the fibres of the vagus also, abolishing the conductivity of the centrifugal cardio-inhibitory fibres and leaving unaffected the centripetal fibres connected with the respiratory and vaso-motor centres. Moreover, the centrifugal vasodilator fibres are more rapidly depressed by cocaine than are the vasoconstrictors.

A difference in the reaction of the different types of fibres must, therefore, be conceded. Moreover, the greater susceptibility to cocaine manifested by the sensory fibres is only the maximal expression of a general law, for these two kinds of fibres exhibit a similar behavior toward the general anæsthetics (*Pereles u. Sachs, Jotcyko u. Stefanowska*) and also toward aconitine (*Dixon*). As a matter of fact, the same law holds good for the behavior toward drugs of the sensory and motor elements of the cord and brain, for ether, chloroform, etc., paralyze the sensory side of the spinal reflex arc and the sensory portion of the cerebrum before the motor excitability disappears (see p. 57 ff). It appears, therefore, that all sensory nervous elements are, as a rule, more readily depressed by chemical reagents than are the motor elements.

Action on Other Tissues.—Although, as shown above, cocaine electively poisons the sensory nerve-endings and fibres, it never permanently damages the other tissue cells unless too concentrated solutions are applied.* Other local anæsthetics closely related to cocaine, such as members of the orthoform group and stovaine, are not so free from such side actions.

Actions on the Vessels.—These are the only organs besides the nerves which are markedly affected by the local action of cocaine. They are strongly constricted, and thus the blood supply at the point of application is markedly diminished. Under its influence hyperæmic and swollen mucous membranes become pale and the swelling diminishes or disappears. This vasoconstricting action of cocaine is often of great value, as for example by rendering sinuses and cavities lined with mucous membrane (such for example as the nares) more accessible

* [The cornea is especially likely to be damaged by too concentrated solutions.—Tr.]

for surgical procedures. The anæmia also reinforces the anæsthetizing action of cocaine by retarding its absorption from the tissues into the blood, and thus keeping it for a longer time at the point of application. The great influence on the induction of local anæsthesia which is exerted by variations in the blood supply of the tissues is well shown by the fact that inflammatory hyperæmia of the eye renders its anæsthetization by cocaine much more difficult, and may in fact entirely prevent it. On this account, the addition of epinephrin to the cocaine solutions often greatly augments the local anæsthetic action. A number of the substitutes for cocaine do not possess this vasoconstricting power, while some of them directly counteract the vasoconstricting action of epinephrin. Cocaine's superiority in this particular over many of its substitutes is a point of much practical importance.

Systemic Action.—In systemic poisoning by cocaine the depression of the sensory nerve-endings is not observed. It cannot, therefore, be considered as comparable to a drug possessing a "curare action" on the sensory nerve-endings, for, when equally distributed throughout the body by the blood, these nerve-endings are not the first elements to be affected, but, on the contrary, the central nervous system is the first organ to be affected. Only by the local application, which brings the cocaine in relatively high concentration in direct contact with the sensory nerve-endings and trunks, is it possible safely to abolish the function of these nervous elements. The great susceptibility of the central nervous system is responsible for the toxic effects which are observed in case too large amounts of cocaine are applied and absorbed.

The action on the central nervous system consists in a primary stimulation and a secondary depression of certain tracts, regions, and functions, while others are depressed from the start. In the higher laboratory animals, very small doses cause the appearance of symptoms of excitation of the cerebral cortex, great restlessness, hallucinations, and uncontrollable motor activity. In man also, larger but not too large doses (maximal dosage 0.05 gm. per dose, 0.15 gm. per diem) [few American authors would consider 0.05 gm. ($= {}^{5}/_{6}$ gr.) a permissible dose.—Tr.] cause confusion, tendency to laughing, etc., a cocaine "Rausch,"* and finally delirium. This stimulating effect on the cortex no doubt is one of the reasons why coca leaves are used in South America as a stimulant or means of enjoyment (Genussmittel), while the suppression of sensations of hunger, emphasized in all reports concerning this custom of the South American natives, is doubtless due to the blunting of the sensibility of the nerves of the stomach.

Therapeutically cocaine has been administered internally to alleviate gastric pain and to relieve nausea of gastric origin. In conditions of mental depression, and especially during the withdrawal of morphine, attempts have been made to utilize the power of stimu-

* Rausch is the German equivalent of the slang term "jag."

lating the cortex possessed by small doses of cocaine. It was, however, quickly apparent that the danger of habituation was equally as great with cocaine as with morphine, and perhaps greater, and that the therapeutic use of cocaine in such cases led to a cocaine habit.

TOXICOLOGY

Toxic Action in Animals.—In warm-blooded animals the first stage of poisoning by cocaine is characterized by restlessness, excitement, and motor activity, followed by clonic convulsions and unconsciousness. The pulse is accelerated (accelerator stimulation), the blood-pressure raised, the pupils dilated (stimulation of sympathetic nerve-endings), and the body temperature is increased. In dogs it may be shown that these convulsions are of cortical origin, for *Feinberg* and *Blumenthal* found that they did not occur after previous extirpation of the cortex, nor were they to be seen in new-born puppies in which the cortical tracts are unexcitable. The convulsive stage is followed by a paralytic stage, with deep coma, loss of sensibility and power of moving, disappearance of the reflexes, and finally by death due to paralysis of the respiratory centre [and also of the vasomotor centres.—Tr.].

The symptoms of poisoning in man vary with the dose and especially with the rapidity of absorption. When very toxic doses are gradually absorbed, the poisoning is characterized by unconsciousness, convulsions, and dyspnœa. At the start the preponderance of excitation may cause maniacal behavior or epileptiform convulsions, with extreme pallor, dilated pupils, and exophthalmos. When large enough doses are very rapidly absorbed, as occurs when strong solutions are applied to eroded mucous membranes, the poisoning may develop with very few symptoms, the victims suddenly fainting and becoming extremely pale and, after convulsions lasting but a short time, dying within a few minutes. With rapid absorption, such as may occur after subcutaneous injection, as little as 0.05 gm. may cause serious poisoning.

The insufficient recognition of the fact that the rapidity with which cocaine is absorbed varies markedly according to the method of application and the condition of the mucous membranes has led to a belief that different individuals exhibit a very different susceptibility to this drug. Many cases of apparent idiosyncrasy should, however, be interpreted as due solely to especially rapid absorption,* as has been emphasized by *Braun*.[3]

The treatment of acute cocaine poisoning is purely symptomatic. While anæsthetics or narcotics may be employed to control the convulsions, it must not be forgotten that their administration augments the danger from the paralysis which develops at a later stage. With threatening cessation of respiration, artificial respiration should be instituted. It goes without saying that, whenever possible, the effort

* See in this connection the relationship between the actions of cocaine and epinephrin, pp. 159, 575).

should be made to prevent the further absorption of the poison. In a case where the drug has been injected into an extremity, this is best accomplished by checking the circulation here by a tight bandage, and after its introduction into any of the body cavities by washing them out in the endeavor to remove any portions not yet absorbed.

Avoidance of Rapid Absorption.—The poisonous effects on the central nervous system occur only when the drug is present in the blood in a certain concentration, which need never be attained when the drug is administered for its local effects, if, by use of proper methods, the drug is so administered as to permit a gradual, and to prevent a too rapid, absorption. Under these conditions such portions of the drug as enter the circulation are excreted, and, what is still more important, that portion which remains for a sufficient time in contact with the tissues is destroyed or altered by them.

Distoxication.—The rabbit after receiving a poisonous dose of cocaine excretes no unaltered cocaine, while the dog excretes only 5 per cent. of the amount administered (*Wiechowski*). Anything which causes a retardation of the absorption and thus secures for the organs time to distoxicate the amounts gradually absorbed is, therefore, of the greatest service in lessening the danger of poisoning. This has been demonstrated by *Kohlhardt*, *Klapp*, and *Kleine*, who injected ordinarily lethal doses of cocaine into the leg of a rabbit after previously tightly applying a rubber tube about the extremity. Under these conditions the longer the constriction was maintained the more mild was the course of the poisoning. In an entirely similar manner, otherwise fatal doses of cocaine may be injected without danger if the paths of absorption are closed by adding to the solution epinephrin, our most powerful vasoconstricting agent. In such case the cocaine leaves the tissues very slowly, as they have thus been rendered nearly bloodless, and enters the circulation only gradually.

PRINCIPLES GOVERNING THE ADMINISTRATION OF COCAINE

So long as the entrance into the blood of cocaine and its distoxication keep pace with each other, relatively large amounts may be administered. If this be borne in mind, the theoretical basis for the different methods of administration is readily arrived at. The indication is to apply the cocaine in sufficiently concentrated form to the peripheral nervous elements which are to be anæsthetized, and to keep it there long enough to prevent its too rapid absorption. This indication is met mainly in two ways. First, by using the weakest solution which will produce a complete anæsthesia and augmenting its effect by bringing it in intimate contact with the nerve-endings and prolonging the period of its contact with them. These are essentially the principles involved in infiltration anæsthesia. The second method consists in using relatively high concentrations but limiting their action to the neighborhood of the nerve-trunks. With both methods the addition of epinephrin to the cocaine solutions diminishes the danger of systemic poisoning.

1. Surface anæsthesia of the mucous membranes, wounds, etc., may be secured by simply dropping on them solutions of cocaine or by applying the solutions with a brush or in cotton tampons and by

similar simple methods. Anæsthesia thus induced is a terminal one,—*i.e.*, one affecting only the terminal sensory nervous elements. When the solution can remain for only a short time in contact with the mucous membrane,—as, for example, when it is used for operation on the nose or throat,—as a rule, concentrated solutions, 10–20 per cent. [!! Tr.],* must be applied. On the other hand, for superficial anæsthesia of the cornea a 2 per cent. solution is sufficient. As a solution injected into the bladder or urethra may remain longer in contact with the mucous membranes, 2–5 per cent. solutions are strong enough. The danger of systemic poisoning increases with the extent of the mucous membrane to which the solution is applied and with its power of absorption, and it should be remembered that this danger is the greatest when the mucous membrane is hyperæmic and especially when it is ulcerated. The addition of epinephrin to the solutions retards the absorption without lessening the depth or duration of the anæsthesia.

In the Eye.—The tissues of the eye present such favorable conditions for the absorption of the anæsthetic that in two minutes after dropping in a little 2 per cent. solution complete insensitiveness is secured. Accompanying this are dilation of the pupil, protrusion of the eye, and widening of the palpebral fissure, all due to stimulation of the sympathetic.

2. Hypodermic and Endermic Injections.—Originally 1 to 5 per cent. solutions were used for subcutaneous injections. Here the anæsthesia is in part a terminal one and in part dependent on blocking of the conducting fibres. As cocaine is very rapidly absorbed from the subcutaneous tissues when its absorption is not artificially prevented,—as, for example, by an Esmarch bandage,—the use of such concentrated solutions is almost more dangerous than a chloroform anæsthesia. By using weaker solutions the danger from absorption may be lessened without interfering with the induction of complete local anæsthesia.

Infiltration anæsthesia (*Schleich*) consists in infiltrating the skin over the region to be incised by means of endermal injections of cocaine solutions and then infiltrating the lower layers one after another. When the solution is thus brought into such intimate contact with the nerve-endings in the field of operation, a satisfactory anæsthesia may be obtained by the use of very dilute solutions which are just strong enough to anæsthetize the nerve-endings, but the anæsthesia does not extend beyond the infiltrated area, for the dilute cocaine solution is efficient only at the point of application. *Schleich* recommended adding to the 0.1–0.2 per cent. cocaine solution only 0.2 per cent. of NaCl, as he believed that the hypotonicity of the solution, by causing a certain amount of "imbibition" anæsthesia (see p. 120), would increase the effect of the cocaine. At present the general preference is

* [The careless use of such strong solutions may readily result in serious poisoning; 5ɱ of 20 per cent. sol. = 1 gr.—Tr.]

for the addition of 0.8 per cent. NaCl, as advised by *Braun* and *Heinze*, with the object of avoiding any damage to the tissues. *Schleich's* solutions contain morphine, but, as morphine has no local anæsthetic powers, the morphine may just as well [or better.—Tr.] be injected before or after the operation.

Nerve Blocking.—Infiltration anæsthesia, however, is not applicable in all conditions or situations. For example, the pain caused by the numerous injections into inflamed tissues prevents its use under such conditions. When such is the case, the method of nerve blocking (*conduction anæsthesia*) is indicated, a method in which the danger of systemic poisoning from absorption is avoided in a different fashion. The injection of a small quantity of a solution of cocaine under the sheath of a nerve and between the nerve-fibres causes an immediate interruption of their conductivity. As, however, endoneural injection usually succeeds only when the nerve-trunk has first been exposed, as a rule recourse is had to perineural injection, which necessarily demands a stronger solution than the endoneural application.

This nerve blocking, which causes a regional anæsthesia, is useful for many and various operative procedures, and is especially adapted to dentistry (*Peckert*). It is also particularly adapted to the anæsthetization of fingers and toes, where its effects should be augmented by the use of epinephrin or tight bandaging. Even major operations, for example, those involving the breast or the thorax, where the intercostal nerves may be "blocked," may be performed painlessly with the aid of perineural injections (*Hirschl*).

Circular anæsthesia according to *Hackenbruch's* method is a third method, occupying an intermediate position between infiltration anæsthesia and regional anæsthesia. Here the tissues surrounding the field of operation are injected in a continuous irregular circle in such fashion as to block all the sensory nerves supplying the part.

3. Spinal Anæsthesia.—Here the cocaine acts on the sheathless nerve-roots as they emerge from the cord and on the nerve-trunks lying in the lumbar dural sac, which are bathed by the anæsthetizing solution, a nerve blocking resulting.

Medicine owes the introduction of this method to *Bier*, of Berlin. The injection in man of 0.005–0.03 gm. of cocaine into the lumbar subdural space is quickly followed by paræsthesia, and soon afterward (in 5 to 10 minutes) by abolition of the pain sense in the lower portion of the body, the sensation of touch, the power of motion, and the reflexes still persisting. With further development of the action the excitability of the other sensory paths is abolished, and after still larger doses there occur motor weakness and paralysis of the lower half of the body. Here the cocaine clearly acts more strongly on the sensory than on the motor elements. The undesirable and often dangerous side actions, which have not infrequently been observed in lumbar anæsthesia, are all probably due to a spreading of the

cocaine inside the dura up along the cord until it can act directly on the higher vital centres. For this reason, it is especially important in lumbar anæsthesia that we should be able to substitute for cocaine some less toxic substance.

By a new method, SACRAL ANÆSTHESIA (*Stoeckel, Läwen, Schlimpert*), in which the cocaine solution is injected into the sacral canal, the attempt has been made to block the spinal nerve-roots after they emerge from the dura. This method is employed chiefly by gynæcologists for special indications. As is self-evident, it is necessary to use stronger solutions here than when they are injected intradurally, otherwise the well-developed nerve-sheaths will not be penetrated by the cocaine in effective amounts.* On the other hand, as the cord is protected from the drug [and as the cocaine cannot pass up alongside of the cord to the vital centres.—TR.], the side actions are much less pronounced (*Schlimpert*).

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[2] Braun: Die Lokalanästhesie, Leipzig, 1905, p. 49.
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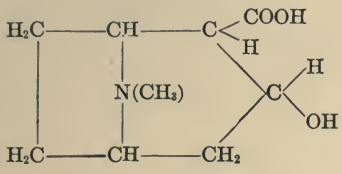
* Novocaine bicarbonate, on account of its rapid diffusibility, is especially adapted for this method (see p. 122).

SUBSTITUTES FOR COCAINE

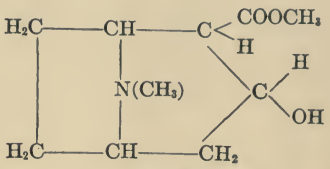
Starting from a knowledge of the constitution of cocaine, by systematic study of the question as to which atom groups cause the action on the sensory nerves and how the reciprocal relation of these groups affects this action, it has been possible to synthetize a considerable number of substitutes for cocaine. These substitutes, generally speaking, possess the advantage of being, when used in equal concentration, cheaper, less toxic, more stable in solution, and of being more readily sterilized, but they are also less powerful anæsthetics than cocaine. They can often replace cocaine in practice or be used as adjuvants to it.

CONSTITUTION OF COCAINE

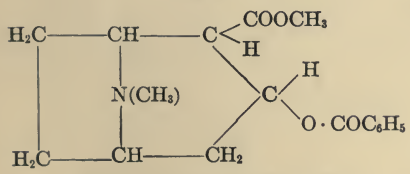
Strong alkalies decompose cocaine into the base ecgonine, methyl alcohol, and benzoic acid.



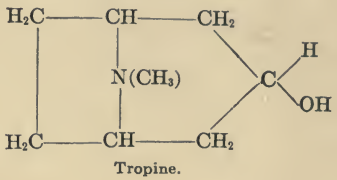
Ecgonine.



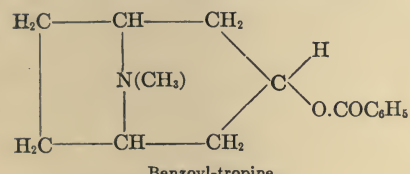
Methyl-ecgonine.



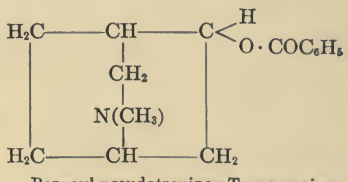
Benzoyl-methyl-ecgonine=Cocaine.



Tropine.



Benzoyl-tropine.



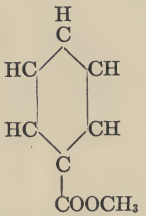
Benzoyl-pseudotropine=Tropacocaine.

Methyl-ecgonine is inactive, being rendered active only when a benzoyl radical is introduced (*Filehne, Ehrlich u. Einhorn*). According to the former author, not all acid radicals produce this effect, for the substitution for the benzoyl radical of other aromatic acid radicals weakens the anæsthetic activity, and it is completely abolished by the substitution of aliphatic acid radicals. Furthermore the discovery, in Javanese coca leaves, of TROPACOCAINE, the basic nucleus of which, pseudotropine, also contains the benzoyl group, has emphasized the importance of this group for the specific activity of these substances. As a matter of fact, *Filehne* was able to demonstrate the local anæsthetic powers of other benzoylated alkaloids,—*e.g.*, benzoyl-tropine. From these facts it may be concluded that the specific local anæsthetic action is due to the combination

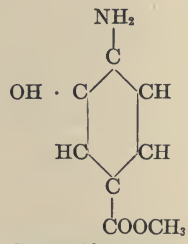
of certain nitrogenous basic substances with the benzoyl radical. If the basic complex contains a COOH group, as is the case with ecgonine, its acid nature must be overcome by esterfication with a methyl or ethyl radical or with some other aliphatic radical (*Poulsson*).

Einhorn's[1,2,3] investigations have shown that local anæsthetic power is a common property of all basic esters of benzoic acid, although it varies in individual cases to a marked degree. While many other aromatic esters also possess this power, a practical importance is possessed only by those compounds which exert a sufficient degree of local anæsthetizing action without damaging the tissues. In addition a sufficient solubility in water is essential for their subcutaneous and intradural administration.

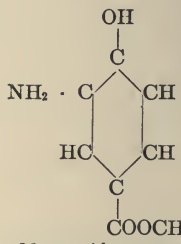
Orthoform Series.—*Einhorn* and *Heinz,* by investigating the action of very simply constituted derivatives of benzoic acid, $C_6H_5.COOH$, and of oxybenzoic acid, $C_6H_4OHCOOH$, in which the very complicated nitrogenous basic radical of cocaine, tropacocaine, etc., was replaced by the amido group, obtained the various orthoforms. These are substances which are but slightly soluble in water and which are much used as analgetic dusting powders.



Benzoic acid, methyl ester.

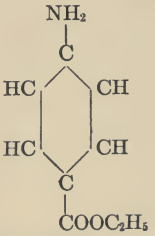


Para-amido-meta-oxy-benzoic acid methyl ester, Orthoform.

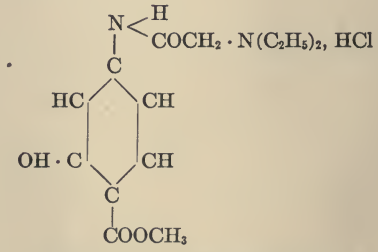


Meta-amido-para-oxy-benzoic acid methyl ester, Orthoform, new.

Other numbers of this group are the more soluble Nirvanin and Anæsthesin (*Dunbar, v. Noorden, Spiess*).



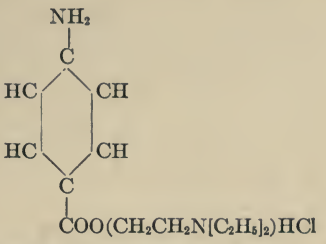
p-amidobenzoic acid methyl ester, Anæsthesin.



The hydrochloride of diethyl p-amido-o-oxy-benzoic acid methyl ester, Nirvanin.

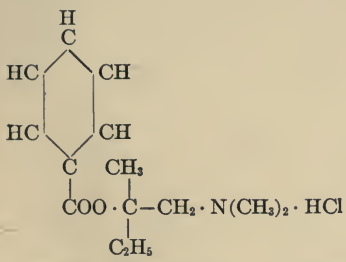
Novocaine.—Another group of active local anæsthetics have been discovered in benzoyl derivatives of the amino-alcohols which were first investigated by Einhorn. Among these is novocaine (*Einhorn*[4]),

which appears to be the best of the cocaine substitutes (*Biberfeld, H. Braun*).

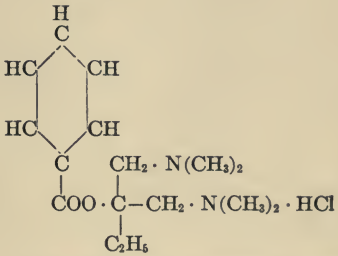


The hydrochloride of p-amido-benzoyl-diethyl-amidoethanol, Novocaine.

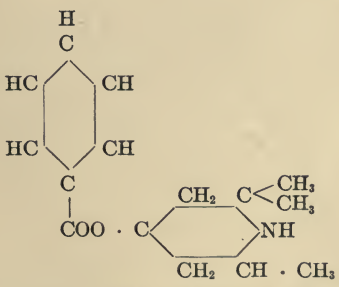
STOVAINE (*Fourneau*), ALYPIN (*Impens*), and EUCAINE also belong to this series. The lactate of beta-eucaine is sufficiently soluble and is much used.



The hydrochloride of dimethylamidoben-zoylpentanol, Stovaine.



The hydrochloride of tetramethyldiamino-benzoylpentanol, Alypin.



Trimethylbenzoyl-oxypiperidine = Eucaine B.

COMPARATIVE VALUES OF THE SUBSTITUTES FOR COCAINE AND THEIR USES

The synthetic cocaine substitutes may be *sterilized,* are fairly *stable* in solution, and are all *less toxic* to the central nervous system than cocaine. According to *Brocqu,* tropacocaine and novocaine are

only *half as toxic* as cocaine and beta-eucaine is even less so, but their *anæsthetic action is also weaker. It would appear that the toxicity for the central nervous system runs parallel with the anæsthetic action on the nerve-endings.*

TROPACOCAINE (*Chadbourne*), derived from the Javanese coca leaves, while less toxic is also much more evanescent in its local anæsthetic action, but may be used if the circulation is interrupted by a tight bandage or by pronounced cooling. On account of its relatively slight toxicity, it has recently been used in preference to cocaine for spinal anæsthesia. In the eye it causes slight mydriasis and no irritation.

BETA-EUCAINE (*Vinci*) is also much less toxic than cocaine, its toxic dose being three times as large. It possesses the disadvantages of being somewhat irritant and of causing local hyperæmia.

STOVAINE is much used for intradural anæsthesia, especially in France (*Challamel*), but it is not altogether harmless to the tissues, for, in the presence of alkaline carbonates, the insoluble carbonate of dimethylamidobenzoylpentanol is precipitated. The carbonate of its homologue, ALYPIN, being soluble, this drug does not cause local irritation (*Braun*[2], *Läwen*[2]).

While the anæsthesia produced by NOVOCAINE is more evanescent than that produced by cocaine, it apparently does not damage the tissues and is considered by many to be the best of the cocaine substitute (*Brocqu, Gros, Braun,*[1] *Heinecke,* and *Läwen*[1]).

ORTHOFORM and others of this group are not substitutes for cocaine, but are rather to be considered as complementary substances (*Spiess*). Most of them being rather insoluble, they are not adapted for subcutaneous use, and even when soluble, as is the case for example with nirvanin, their anæsthetic action is too weak for them to be of value when thus administered. On the other hand, orthoform is employed as a rather insoluble dusting powder for wounds and ulcers. As it penetrates the skin and mucous membranes with difficulty, it relieves pain only when brought in contact with exposed nerve-endings, in which case its action is rather prolonged. It should, however, be used cautiously, for it may produce other undesirable local effects, such as œdema, eczema, and gangrene, especially when used in the treatment of ulcers of the leg. It also transforms oxyhæmoglobin into methæmoglobin, even in a dilution of 0.02 per cent. It should, therefore, not be used in the treatment of open wounds or of gastric or intestinal ulcers, nor should it be injected into the tissues (*Fröhlich*).

ANÆSTHESIN is employed in the same way as orthoform, and causes a prolonged local anæsthesia, apparently without producing the harmful effects seen with orthoform. In the form of its p-phenolsulphonate, SUBCUTIN, it may be administered subcutaneously, but is very irritant locally (*Braun*[3]).

The differences in action between cocaine and its above-mentioned

substitutes, many of which are still in the experimental stage, are to some degree qualitative as well as quantitative, for when applied to mixed nerves all of them do not appear to exert so elective an effect on the sensory nerves as does cocaine. Stovaine, for example, in dilute solution strongly depresses the motor nerve-endings (*Santesson*). In judging of their value, the most important points are the rapidity with which recovery of normal function occurs after their employment and the extent to which they cause permanent damage to the nerves. In these respects also cocaine apparently is superior to all its substitutes with the exception of novocaine (*Läwen*[1]). In addition the value of many of these drugs is impaired by the fact that they (*e.g.*, eucaine and tropacocaine) dilate the vessels, and thus lessen or prevent (*Läwen*[2,3]) the favorable effect of the addition of epinephrin.

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CHAPTER IV

PHARMACOLOGY OF THE VEGETATIVE NERVOUS SYSTEM

THUS far we have discussed only the so-called animal nervous system, and the manner in which pharmacological agents may influence the functions of its various parts, the sensory nerve-endings, the cerebral, medullary, and spinal centres, and the efferent nerves which carry motor impulses to the voluntary striped muscles. We have taken these up in a particular order, believing that by so doing we have laid the foundation for a clearer understanding of the manner in which pharmacological actions should be analyzed.

THE VEGETATIVE NERVOUS SYSTEM

In opposition to the animal nervous system, which is under the control of the will, stands the so-called vegetative system, the efferent nerves of which supply those organs whose functions are not under the control of the will. These are the glands and the organs containing smooth muscles, such as the viscera, the vessels, the smooth musculature of the skin, the iris, etc. Physiologically similar to these organs with smooth muscle are certain striated muscles,—viz., those of the heart, the œsophagus, and the penis, and in certain animals the iris, which, in the birds for example, is composed of striped muscle. The characteristic quality of the innervation of all these tissues is due to the fact that their functions, although they may be influenced through the central nervous system, are able to continue independently of it. The nervous system which innervates them possesses a certain, although limited, independence of the central nervous system, and has consequently been named by *Langley* the AUTONOMIC NERVOUS SYSTEM. However, we shall retain the name, vegetative nervous system, and use the term autonomic (parasympathetic) only for that portion of the vegetative system which does not arise from the sympathetic trunk.*

The efferent fibres of the vegetative nervous system reach their terminal organs—the muscles of the circulatory, digestive, and sexual organs and the glands, etc.—through nerves which emerge from peripheral nerve-ganglia. While vegetative nerve-fibres originate in the central nervous system, it is characteristic of the vegetative nerves that they never pass directly from the central nervous system to the periphery, without first connecting, during some portion of their course, with ganglion-cells.

SYMPATHETIC NERVOUS SYSTEM.—Differing both anatomically and

* [For this system *Langley* has more recently suggested the name parasympathetic, and this term will also be used in this work.—TR.]

embryologically, as well as physiologically and pharmacologically, from the other vegetative fibres is the group of sympathetic fibres, which emerge from the middle portion of the spinal cord in the thoracic and the first 4 or 5 lumbar nerves and pass through the white *rami communicantes* to the sympathetic trunk and to the superior and inferior cervical and the stellate ganglia, from which ganglia they join the spinal nerves through the gray *rami communicantes*. These sympathetic nerves supply the vessels, glands, and smooth-muscled organs throughout the body and form a homogeneous portion of the vegetative nervous system.* In the accompanying diagram (p. 139) these nerves are colored red.

Autonomic or Parasympathetic System.—However, almost all these organs, as indicated by the nerves colored blue in the diagram, also receive another sort of vegetative nerves, some of which arise from the brain and medulla, and others from the sacral cord, and which are called by us the cranial and the sacral autonomic (parasympathetic) nerves. Autonomic nerves also arise from the midbrain, which run in the oculomotorius to the ciliary ganglion, from which they pass as the short ciliary nerves to the sphincter of the iris and the ciliary muscle.

In the chorda tympani are secretory fibres for the salivary glands, and vasodilator fibres for the oral cavity, which are autonomic nerves arising from the medulla. The facial and glossopharyngeal nerves also contain secretory and vasodilator fibres, which pass into the trigeminus and supply the oral, nasal, and pharyngeal mucous membranes. Finally, autonomic fibres emerge from the medulla oblongata and run in the vagus to the viscera. These are the cardio-inhibitory fibres, constrictors for the bronchial muscles, motor fibres for the œsophagus, stomach, and intestine, and secretory fibres for the stomach and the pancreas. This autonomic system may be named the cranial-bulbar or, briefly, the cranial autonomic system. Its influence is most powerful at the oral end of the alimentary canal and in the neighboring structures of the head, and from there down diminishes in extent and intensity. Near the anal end of the alimentary canal it is replaced by the sacral autonomic system, the fibres of which pass from the cord in the first sacral nerve, and, as the nervus pelvicus, supply the lower portion of the alimentary canal—the descending colon, rectum, and anus—as well as the bladder and genital organs.

A third nervous mechanism controlling the automatic movements of the hollow viscera, such as the intestine, has received from *Langley*

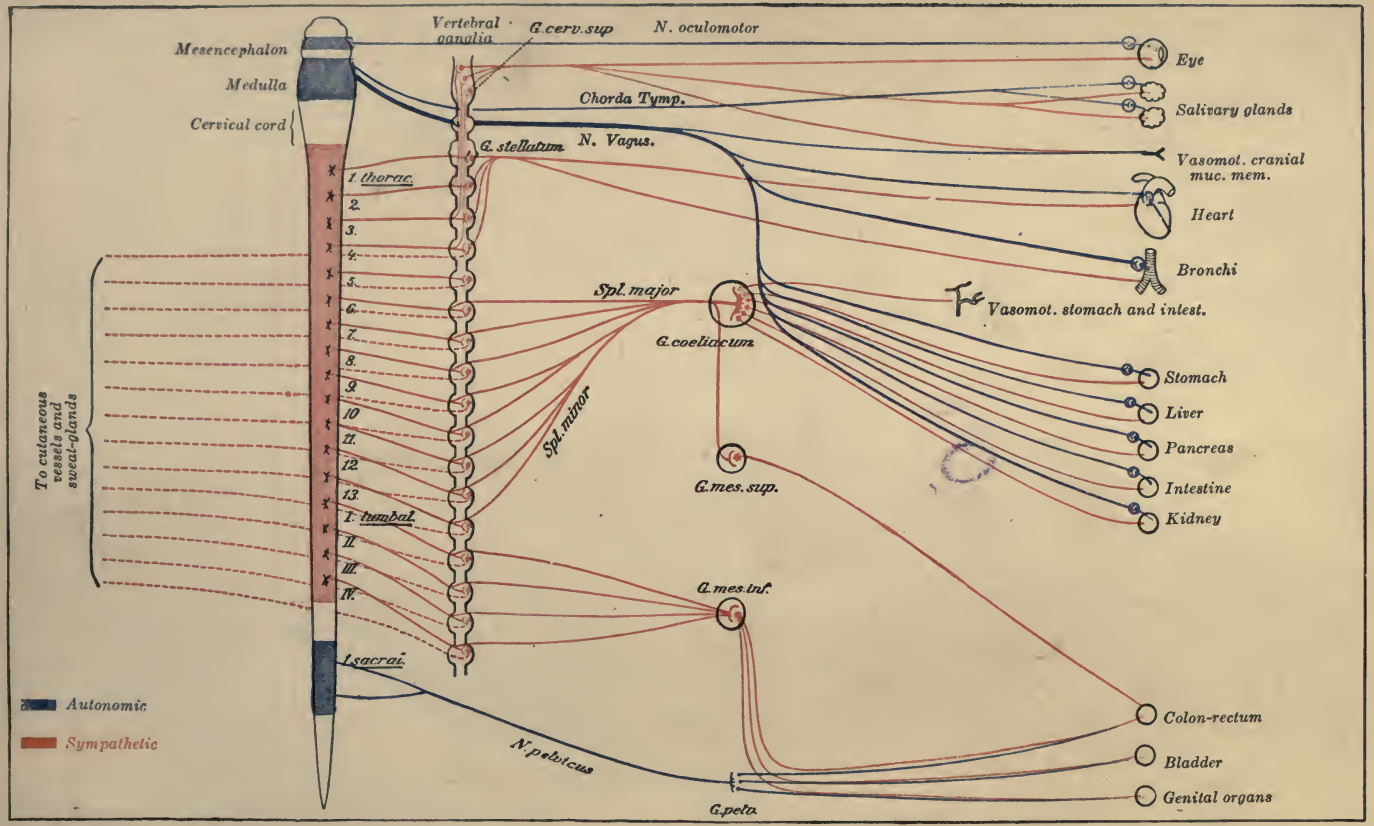
* As a result of the labors of *Gaskell*, *Langley*, and others, our knowledge of the structure and function of the sympathetic and of the other autonomic systems has undergone a complete transformation in recent years. The following description is based on the views developed by *Langley*, which may be found as described by him in Schaefer's text-book on physiology, 1900, vol. 2, p. 516, and in Asher-Spiro's Ergebn. d. Physiologie, 1903, vol. 2, p. 808. The nomenclature followed, however, is the one indicated above.

the name of the "ENTERIC SYSTEM." These are peripheral automatic centres, which, however, receive impulses from the central nervous system through autonomic and sympathetic fibres.

All the sympathetic nerves form a physiological unit, and everywhere their nerve-endings exhibit one common pharmacological reaction (to epinephrin). According to *Langley,* on the other hand, the cranial and the sacral autonomic systems belong together in a physiological sense. This physiological relationship is most strongly demonstrated by their similar reaction to a number of drugs and poisons, to which we will later turn our attention. Pharmacologically the cranial and sacral autonomic systems exhibit a distinct contrast to the sympathetic system, just as they do in respect to their functions, and this too in spite of the fact that both types of vegetative nerves appear to be essentially similar in structure.

However, all the vegetative nerves, in accordance with this similar structure, possess one pharmacological reaction in common, the discovery of which was a decisive step toward the recognition of their true nature. This is their reaction to nicotine, which exerts an elective action on one particular portion of all vegetative nerves. In accordance with the general scheme of their arrangement, the vegetative nerve-fibres, unlike those of the animal system, never pass directly from the central nervous system to their terminal organs, but, after leaving the gray matter of the central nervous system, pass into ganglia in which the central fibres terminate, coming at this point into close relationship with the ganglion-cells, from which new nerve-fibres then pass down to the terminal organs. These separate fibres are consequently named the pre-ganglionic and the post-ganglionic fibres. The course of the vegetative nerves is always interrupted in a ganglion, and in the whole course of the nerve only in a single ganglion, where there is, as it were, a switching of the impulse from the pre-ganglionic to the post-ganglionic fibres. This interruption of the impulse may occur in the first ganglion through which the nerve passes,—for example, in one of the vertebral ganglia, which, like the spinal ganglia, are segmentally arranged in the sympathetic trunk. Other vegetative fibres, however, pass through a first and often a second ganglion, which may be interposed in their path, without branching in them, and terminate only in more peripherally situated prevertebral ganglia,—for example, the nerve fibres of the splanchnicus terminate in the solar plexus and those of the pelvic nerve in the hypogastric plexus, while others may terminate in still more peripherally lying ganglia, which are situated directly in the terminal organs.

The vertebral ganglia, with the exception of the superior and inferior cervical ganglia, supply the vegetative organs of the skin and the trunk and extremities, which include the glands, the vessels, and the smooth muscles of the skin, while the prevertebral ganglia supply exclusively the viscera. The stellate and the superior cervical ganglion, which may be looked upon as resulting from the fusion of vertebral and prevertebral ganglia, supply both viscera and skin.


Mesencephalon
Medulla
Cervical cord
Vertebral ganglia
G. cerv. sup
N. oculomotor
Eye
Chorda Tymp.
Salivary glands
G. stellatum
N. Vagus.
Vasomot. cranial muc. mem.
Heart
Bronchi
1. thorac.
2.
3.
4.
5.
6.
7.
8.
9.
10
11.
12
13.
1. lumbal.
II.
III.
IV.
1. sacral.
Spl. major
Vasomot. stomach and intest.
G. coeliacum
Spl. minor
Stomach
Liver
Pancreas
Intestine
Kidney
G. mes. sup.
G. mes. inf.
To cutaneous vessels and sweat-glands
Autonomic
Sympathetic
N. pelvicus
Colon-rectum
Bladder
Genital organs
G. pelv.

Common Reaction to Nicotine.—No matter at what point the central fibres terminate and this switching occurs, and no matter what the function of the post-ganglionic fibres, whether motor, inhibitory, or secretory, nicotine always, after a primary stimulation, causes a paralysis of this relay station, or ganglion. This is the general rule to which there are no exceptions, although the different ganglia exhibit a variable degree of susceptibility toward this poison and although greater differences are exhibited by different species of animals; for example, nicotine acts far less powerfully on these ganglia in the dog than in the cat or rat.

Langley, by applying a dilute solution of 0.5 per cent. of nicotine to the separate exposed ganglia, produced a localized poisoning, and, using this method, was able to employ this drug as the means of determining whether an efferent vegetative nerve-fibre passed through the ganglion in question without joining it, or whether at the poisoned point the fibre terminated and entered into a physiological union with the ganglionic cells. If stimulation of the nerve at a point lying centrally to the ganglion still produced the same effect as before the application of the poison, it was clear that its nerve-fibres merely passed through the ganglion, but if such stimulation did not produce such effect, it was evident that the nerve-fibres in question terminated in this ganglion, and that the post-ganglionic fibres arose from it. By means of this method, *Langley* was able to demonstrate the interruption of numerous sympathetic and cranial and sacral autonomic nerves in their various vertebral and prevertebral ganglia. One example may serve to make this more readily understood. Stimulation of the cervical sympathetic below the stellate ganglion causes dilation of the pupil, widening of the palpebral fissure, and alteration of the calibre of the vessels and of the secretory functions of the cranial mucous membranes. After application of nicotine to this ganglion the same stimulation produces no vasoconstriction in the upper extremity, but still produces the same effects in the eye and in the cranial mucous membranes. From this it is evident that the vasomotor nerves of the upper extremity enter into some sort of a union with the ganglionic cells, while the nerve-fibres for the pupil and for the cranial mucous membranes pass through this ganglion and do not find their relay station until they reach the cervical ganglia.

After the injection of nicotine into the circulation, stimulation of all pre-ganglionic fibres is ineffective, while stimulation of post-ganglionic fibres causes all the usual effects. This shows that the nerve-fibres and their peripheral nerve-endings remain excitable and that nicotine poisons only the relay stations in the ganglia.

The Antagonistic Functions of the Sympathetic and Autonomic or Parasympathetic Systems.—The action of the nicotine is exerted on all the ganglia of the entire vegetative system, whether their fibres originate from the sympathetic or from the autonomic system, but otherwise these two groups of vegetative nerves in many respects exhibit an antagonistic physiological and pharmacological behavior. In this connection it is a fact of very great importance that most of our organs possess a double innervation, coming on the one hand from the sympathetic system and on the other from the cranial or sacral autonomic (parasympathetic) system, and that almost everywhere, where organs are thus doubly innervated, this double inner-

vation is an antagonistic one, the stimulation of the sympathetic fibres causing the opposite effect from that produced by stimulating the fibres belonging to the autonomic system. For example, the splanchnicus, a sympathetic nerve, inhibits the movements of the intestine, while the parasympathetic fibres of the vagus and the sacral fibres of the pelvicus excite the motor activity of the upper and lowest portions of the intestines. This antagonism is also evidenced by the following physiological facts: Thus, the dilator of the iris is innervated by the sympathetic, while the antagonistic sphincter of the iris is innervated by autonomic fibres in the oculomotorius, and the cardio-inhibitory fibres of the vagus are opposed by the sympathetic accelerans. In short, almost all organs for which a double innervation from both systems has been demonstrated are antagonistically influenced through these systems. There exists, however, a group of organs,—viz., the vessels and glands of the skin—which, so far as our present knowledge goes, appear to be innervated only by the sympathetic system.

Epinephrin a Specific Poison for Sympathetic Nerve-endings.—The different physiological behavior of the two vegetative systems expresses itself also in their reaction to pharmacological agents, there being one group of drugs which act only on the sympathetic nerve-endings, and another which acts on all the various autonomic nerve-endings. Thus, epinephrin, the suprarenal hormone, excites all the nerve-endings which in the accompanying diagram are colored red,—that is, it always produces the same effects on the various organs as are produced by stimulation of their sympathetic nerve-fibres. Owing to this action on the sympathetic nerve-endings, epinephrin causes vasoconstriction in all vascular systems [except the pulmonary and coronary?—Tr.], strengthening and acceleration of the heart-beat similar to that caused by stimulation of the accelerans, dilatation of the pupil like that produced by stimulation of the cervical sympathetic, and secretion of the salivary glands in so far as these glands are rendered active by stimulation of their sympathetic nerves.

Where, however, sympathetic fibres are inhibitory in their functions,—for example, in the stomach and intestine, or in the bladder,—epinephrin does not cause a stimulation, but, on the contrary, an inhibition of their motor functions. Epinephrin always produces the same effect as the stimulation of the sympathetic nerve of any organ, a fact which is especially strikingly demonstrated in those organs in which stimulation of the sympathetic nerves causes in one species of animal contraction and in another relaxation, as is the case for example in the bladder (*Elliot*). It may, therefore, be stated that epinephrin produces excitation only on those vegetative nerve-endings which belong to the sympathetic system.*

* With the single exception of the sweat-glands which react to pharmacological agents as if autonomically innervated.

In ERGOTOXIN, a substance present in ergot, *Dale* has discovered another toxic substance which also exhibits a limited elective affinity for certain of the sympathetic nerve-endings, for it poisons only the nerve-endings of those fibres the stimulation of which causes motor activity, and produces no effect on those causing inhibition. After large doses of ergotoxin a stimulation of vasoconstrictor nerves no longer causes vasoconstriction, the accelerans loses its influence, and so forth, while the inhibitory influence of the splanchnicus on the intestine or of the sympathetic nerves on the bladder, in those animals in which they inhibit this organ, remains unaffected.

SPECIFIC POISONS FOR AUTONOMIC OR PARASYMPATHETIC NERVES.—While epinephrin produces no effect on the cranial and sacral autonomic nerve-endings, there is another group of drugs which act particularly on these organs, leaving the sympathetic nervous system, with one exception, entirely unaffected. The chief representatives of this group are atropine on the one hand and muscarine, pilocarpine, physostigmine, and choline on the other. Of these muscarine stimulates and atropin paralyzes the nerve-endings of the autonomic fibres which in the diagram are colored blue. This antagonism holds good right down the line, muscarine causing miosis, and atropine, by preventing the action of the autonomic oculomotorius, causing mydriasis; on the heart muscarine producing the same effect as stimulation of the vagus, while atropine prevents the action of the vagus and thus enables the influence of the sympathetic accelerator fibres to gain the upper hand, muscarine causing contraction and atropine relaxation of bronchial muscles. Further, muscarine and pilocarpine cause violent contraction of the gastric and intestinal muscles and of the smooth muscles of other organs, while atropine in certain dosage abolishes the tone of these muscles. Muscarine and pilocarpine cause secretion in all true glands; atropine inhibits it. As these drugs also act in a similar fashion on the glands of the skin,—although, as far as is at present known, they are innervated only by sympathetic and not by autonomic nerves,—we have here an apparent exception to the general law of their behavior. However, one can almost believe that this exception is actually only an apparent one, and that it will be explained when more has been learned of the innervation of these glands.

The points at which these different drugs act are not completely known in all their details. This much, however, is certain,—viz., that they all act on the terminal nervous organs of the autonomic nerves, and that this common pharmacological behavior indicates that the different nerve-endings of this system belong together.

Similar pharmacological—which is the same as to say similar chemical—reactions of organs indicate a homologous chemical structure, and consequently such may be assumed for all the sympathetic terminal nervous organs, and also for all autonomic ones. Moreover, the nerves of these two systems appear to differ also in respect to their points of origin in the central nervous system, these centres being also characterized by certain chemical or pharmacological reactions which are characteristic of them. Picrotoxin, obtained from Indian berries (Anamirta paniculata), in addition to producing other effects, stimulates all the cranial and sacral autonomic nerves,—the oculomotorius, the chorda tympani, the vagus, and the pelvicus,—this action being not peripheral but cen-

tral (*Grünwald*). It thus appears that the autonomic centres all exhibit the same chemical reaction. This may not be said of the sympathetic central organs with the same general application, for up to the present there are only a few facts known which indicate that this is probably the case (*Joncscu*).

From the above it may be seen that nicotine acts on all the ganglia of the entire vegetative nervous system, while epinephrin exerts its action only on the sympathetic nerve-endings. Besides the above-mentioned drugs many other substances act on the separate portions of the vegetative system. As, in all doubly innervated organs, the stimulation of one system and the depression of the other must produce similar effects, it is evident that the same alterations of the functions of these organs may result from pharmacological actions exerted on different points. Thus, for example, dilatation of the pupil may be produced either by stimulation of the sympathetic nerve-endings in the iris by epinephrin, or by paralysis of the oculomotorius nerve-endings by atropine, or the action of the heart may be accelerated as a result of stimulation of the accelerator nerve-endings by large doses of caffeine, or by paralysis of the vagus nerve-endings by atropine. It is thus evident that unusually numerous and complicated pharmacological actions on the vegetative nervous system are possible.

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CHAPTER V

PHARMACOLOGY OF THE EYE

PHARMACOLOGICAL REACTIONS OF THE RETINA

The light-sensitive layers of the retina—*i.e.*, the visual cells with their rods and cones—transmit their impulses to the layer of the retinal ganglion-cells through the bipolar cells, which may be looked upon as corresponding to the spinal ganglion-cells, while the retinal ganglionic layer may be considered as a portion of the gray matter of the central nervous system which has been pushed out into the periphery and from which impulses pass via the optic nerve into the brain, just as impulses pass from spinal ganglia through the conducting paths up into the higher portions of the central nervous system.

This preliminary statement appears necessary in order that we may understand why, in the first place, many toxic substances which act on the retinal ganglia also produce changes in the optic nerve which arises from them,* in apparent contradiction to the behavior of the centripetal nerves whose sensory terminal organs in the periphery may be damaged without its being necessary that the nerve itself be injured, and why, in the second place, the retinal elements themselves are acted upon by pharmacological agents whose preponderating actions are ordinarily exerted only on the central nervous system.

Drugs Relieving Retinal Hyperæsthesia.—This is of significance for those cases in which the susceptibility of the retina is abnormally augmented or diminished by photophobia or by retinal amblyopia. Drugs which are certainly able to moderate hyperæsthesia of the retina in photophobia accompanied by severe pain are apparently not known. According to *Simpson*, if the eye be held immediately above chloroform its vapors relieve photophobia, and the same is stated to be true of carbonic acid gas (*Ringer-Thamhayn*).

The symptoms of photophobia are due to stimuli which reach the centres through the trigeminus. They may occur even after previous section of the optic nerve and in the totally blind, and are, therefore, to be considered as due to a reflex occurring within the retina, which here behaves, as it were, as a segment of the spinal cord. They appear to be analogous to the algesias and hyperalgesias of particular regions of the skin which have been described by *Head* as occurring in diseases of the viscera whose innervation is connected with the same segment of the spinal cord as is that of the painful cutaneous area. However, this pain resulting from bright light is often due only to a spasmodic reflex contraction of the sphincter of the iris, and in such cases it disappears when atropine or homatropine is instilled.

* In this connection, among others, may be mentioned the amblyopias due to toxic action of methyl alcohol, quinine, felix mas, pelletierine, and probably also in part those due to tobacco, ethyl alcohol, and carbon disulphide (*Uhthoff*).

Drugs Augmenting Retinal Excitability.—On the other hand, the excitability of the retinal elements may be certainly augmented by STRYCHNINE, which, as we know, possesses the power of increasing reflex excitability in general. Sharpness of vision of both the normal eye and of one impaired as a result of amblyopia may be temporarily increased by this drug. This action takes place chiefly in the periphery but also to a certain extent in the centres, and results in an improvement in the power of differentiating colors (*Dreser*). *This effect may be produced on one side only if strychnine be injected into the temple or instilled into the eye* (*Filehne*). It is just as difficult to determine whether such a temporary augmentation of the excitability of the retinal ganglionic organs can be of value in diseases of the eye as it is to judge of the value of the analogous employment of strychnine in motor pareses.

Santonine.—A peculiar alteration of the perceptive retinal elements of caused by the anthelmintic santonin. About one-half hour after taking this drug, brightly illuminated objects appear violet, and a little later yellow. This is due to a primary stimulation followed by depression of the retinal cells which are susceptible to the violet rays of the spectrum. The central color sense (*complementary perception of violet*) remains (*Knies*).

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PHARMACOLOGICAL ACTIONS ON THE IRIS AND THE CILIARY MUSCLE

We possess a much more exact knowledge of the action of drugs on the motor organs of the internal eye,—*i.e.*, on the muscles of the iris and on the ciliary muscle.

The iris is made up of two sets of muscles, one set being arranged in the form of a ring while the other is composed of radiating muscle-fibres. The circular muscle, the sphincter of the iris, is innervated by the autonomic post-ganglionic fibres coming from the oculomotorius, which send pre-ganglionic fibres to the ciliary ganglion. The antagonistic radial muscle, the dilator of the iris, is innervated by the sympathetic nerve coming from the superior cervical ganglion, from which the post-ganglionic fibres pass to these muscles alongside the ciliary ganglion and via the carotid plexus.

The contraction of the ciliary muscles narrows the ring in which the lens is suspended so that owing to its own tension it can become more convex, The ciliary muscle receives the impulses which produce this effect through the cranial autonomic fibres of the oculomotorius, just as does the sphincter of the iris.

It is claimed by *Morat* and *Doyon*, and denied by *Heese* and others, that nervous impulses are received by the ciliary muscle through the sympathetic which produce the antagonistic effect of widening this ring and rendering the lens less convex. The negative results of the last-named authors cannot, however,

be considered as definitely decisive, because the range of accommodation of the animals used in their experiments is too slight (*Heese, Hess u. Heine*).

Certain drugs produce in both of these muscles stimulation or paralysis as should be expected from their different nerve supply.

The centres of the autonomic oculomotorius which lie in the cerebrum may be affected by pharmacological agents so as to produce changes in the pupil, asphyxia for example causing a paralysis of these centres. Consequently, a sudden maximal dilatation of the pupil serves as one of the latest warnings of danger of asphyxia in the course of anæsthesia.

SUCH DILATATION OF THE PUPIL OF CENTRAL CAUSATION, DUE TO INHIBITION OF THE OCULOMOTORIUS, may result from psychic excitement, such as a sudden fright, or from direct electric stimulation of the cerebral cortex in the region

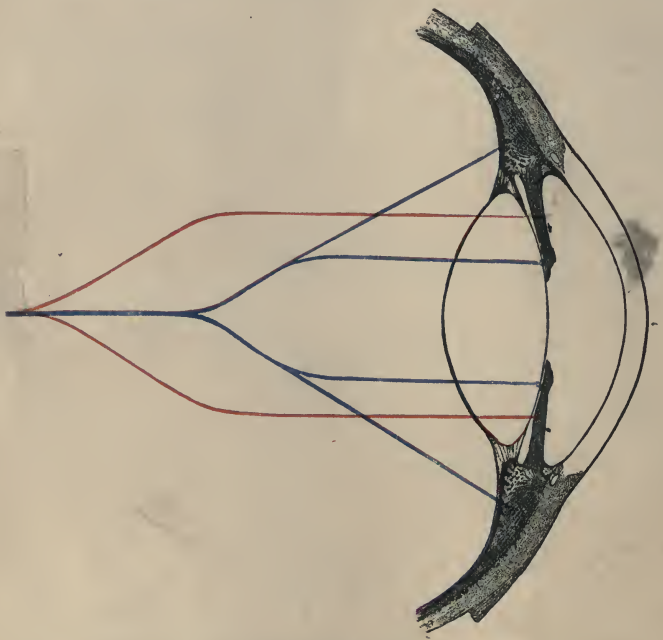

FIG. 8.—Red, sympathetic nerves; blue, autonomic or parasympathetic fibres from the oculomotorius.

of the gyrus sigmoideus or of the basal ganglia, and this may occur when eith the trigeminal nerve, which contains the vasomotor nerves of the iris, or t superior cervical sympathetic ganglia or the cervical cord itself has been severe This reflex dilatation of the pupil can, consequently, be explained only as d to a weakening of the tone of the oculomotorius centre,—*i.e.*, as due to t stimulation of a central inhibitory mechanism (*Braunstein*). If this inhibito mechanism, which is ordinarily kept active by all sorts of sensory stimu becomes inactive as the result of cutting off all sensory stimuli,—as, for examp in natural sleep or that caused by chloral,—the tone of the oculomotorius cent is augmented and the pupil contracts.

In all probability this central autonomic inhibitory mechanism is electively paralyzed by morphine, even in moderate doses which produce hardly any analgetic effects. Consequently a more or less pronounced miosis is a constant symptom of the action of morphine. Atropine overcomes this morphine miosis promptly, but cocaine, whose action is only that of rendering the sympathetic nerve-endings more excitable, hardly alters it (personal communication of *E. Fuchs*). Both of these facts indicate the correctness of the explanation of the morphine miosis given here. It would appear that the autonomic centre of the cardiac vagus is affected in an analogous fashion, and this is probably, therefore, an explanation of the slowing of the heart caused by morphine (*Danilewski u. Lawrinowitsch*). This hypothetical inhibitory centre may be looked upon as being a controlling mechanism for the sympathetic nerves, which acts in opposition to and is opposed by corresponding centres of the cranial autonomic nerves so that they maintain a combined control or balance, just as is the case with the motor centres controlling the agonistic and antagonistic voluntary muscles. (See p. 16 and Fig. 3, p. 17.)

In all probability, therefore, *the miosis of sleep and of morphine poisoning* is due to a markedly augmented—*i.e.*, uninhibited—tone of the oculomotorius centre which normally, in the waking state, is under the influence of strong inhibitory impulses from the cerebral cortex, the corpora quadrigemina, and the corpora striata (*Braunstein*).

Miosis due to excitation of this autonomic oculomotorius centre is one of the symptoms produced by the action of certain central convulsants, particularly *picrotoxin* (*Grünwald*). This is of some interest, inasmuch as this drug electively excites not only the centres of the autonomic oculomotorius but also all other centres of the autonomic nerves known to us, those of the chorda, vagus, pelvicus, etc., from which the conclusion may be drawn that, like their terminal organs, the motor centres controlling the agonistic and antagonistic voluntary muscles have a common chemical structure.

Mydriasis due to paralysis of the oculomotorius centre occurs as a pathognomonic symptom in certain poisonings,—for example, those caused by meat, fish, mussels, cheese, and particularly by that caused by sausage, the so-called botulismus. Here, however, not only the autonomically innervated internal muscles of the eye, the iris and the ciliary muscle, but almost always the external muscles, as well as the levator palpebræ, are affected so that ptosis and usually double vision result. This is a readily recognized difference between the effects of such poisonings and of all other poisonings which cause a mydriasis induced peripherally (*Uhthoff*).

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MIOTICS ACTING IN THE PERIPHERY

The autonomic nerve-endings in the sphincter of the pupil and in the ciliary muscle are stimulated by the drugs of the physostigmine group, of which physostigmine itself is the most important.

PHYSOSTIGMINE OR ESERINE

PHYSOSTIGMINE, or eserine, is an alkaloid occurring in the calabar bean, the fruit of Physostigma venenosum. With sulphuric and salicylic acid it forms readily crystallizable, colorless, hygroscopic salts, whose aqueous solutions after a time acquire a red to dark cherry-red color, as the result of the formation of an inactive oxidation product, *rubreserine*. The calabar bean contains another alkaloid, *eseridine*, with similar action, and still another, calabarine, which possesses a convulsant action.

MIOTIC ACTION.—If a few drops of a 1 per cent. solution of eserine be instilled into an eye, after about 20 minutes the pupil becomes narrow and the ciliary muscle begins to contract. The near point and far point of vision approach each other, and after half an hour the far point approximates the normal near point. After about two hours the spasm of accommodation passes off, but the pupil remains narrow for a considerable time longer. At this time, however, the accommodation is still more excitable than normally and the slightest voluntary effect produces a most extreme degree of accommodation (*Hamer*).

Apparently the action of eserine on the pupil could be explained [illegible] well by a paralysis of the dilator as by a spasm of the constrictor mechanism of the iris, or it might be attributed to both of these effects occurring at the same time. However, it may be experimentally shown that the dilator of the iris retains its excitability, for, if the cervical sympathetic be stimulated in an animal whose pupils are maximally contracted by eserine, they dilate in normal fashion. This, however, does not prove that the tone of the sympathetic nerve-endings in the iris has not perhaps been weakened by eserine. This is, in fact, probable, inasmuch as apparently every stimulation of the sphincters is necessarily accompanied by a relaxation of the dilators, and *vice versa* (*Waymouth Reid*).

The point at which eserine acts is thus seen to lie in the sphincter of the iris and in all probability in the terminal organs of the autonomic oculomotorius, for under certain conditions it can produce contraction of the pupil even after section of the short ciliary nerves or after removal of the ciliary ganglion, but it no longer produces this effect if sufficient time has elapsed since their section to permit the nerve-endings to degenerate. Defined more exactly, its action does not consist in a direct excitation of these elements, but in the production of a very marked augmentation of their excitability. This appears to be indicated by the observations, described below, on the lowering of the threshold value for stimuli which is caused by eserine. It is also in agreement with the fact that after previous section of the oculomotorius,—*i.e.*, after abolition of stimuli from this centre,—eserine produces no apparent effects,—*i.e.*, does not overcome the existent sympathetic tone. Only after section of the sympathetic is it effective and able to narrow the pupil, for then the chemical stimuli furnished by the blood are sufficient to stimulate the terminal organs of the

oculomotorius if they have been rendered over-excitable by eserine. It is important to emphasize this fact, because of the action of eserine in similarly increasing the excitability of the other autonomic (parasympathetic) terminal organs (see below).

Action on Accommodation.—This action of eserine, that of rendering the oculomotorius nerve-endings in the ciliary muscle more excitable, is responsible for the facilitation of accommodation or the spasm of accommodation which may result from its employment. As a result, in addition to rendering it difficult or impossible to see clearly any objects lying beyond the near point, eserine causes one to over-

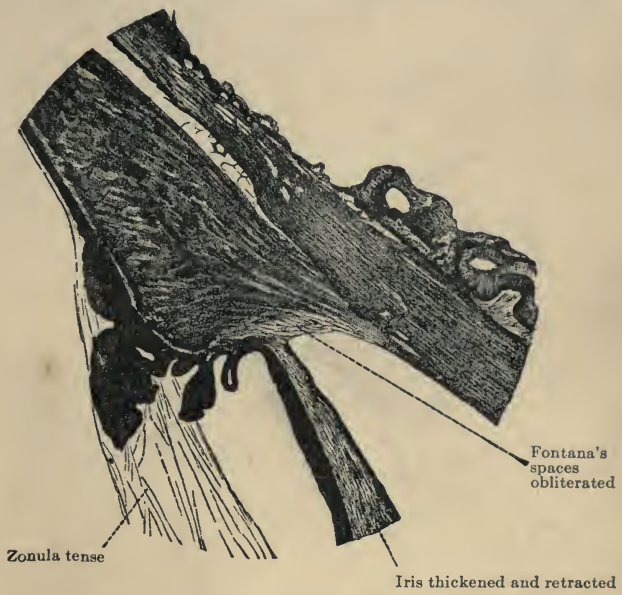

Fig. 9.—Monkey's eye after atropine (Heine).

estimate their size (macropsia), because, on account of the slighter effort at accommodation they are held to be more distant and, as the angle of vision remains the same, they are held to be larger.

Effect on Intra-ocular Tension.—Another result of the action of physostigmine in the eye is much more important; this is the diminution of the intra-ocular pressure (*Laqueur*). This is chiefly the result of the widening of Fontana's spaces which results from the concentric movement inward of the ciliary body, as a consequence of which the outward passage of vitreous fluid is markedly facilitated. Figs. 9 and 10, representing preparations of monkey's eyes fixed, one with the ciliary muscle relaxed and the other with this muscle contracted, illustrate this action. This effect is aided by the contraction

of the internal blood-vessels of the eye caused by eserine, which thus lessens the secretion of the vitreous humor (*Laqueur*).

According to *Grönholm*, in rabbits this action on the vessels is the only cause of the diminution of pressure. *Knape*, on the other hand, found that eserine, like atropine, always caused an active hyperæmia of the rabbit's iris and no alterations in the blood-vessels of the fundus. Moreover, in his experiments on the normal eye, which were carried on with the observation of every precaution against error, he never, with the exception of very temporary variations at first, was able to observe any alteration of the intra-ocular tension, neither diminution in eserine miosis nor an increase in atropine mydriasis, observations which are explained by the assumption that the regulatory mechanism of the normally functioning eye prevents such effects. When this is disturbed, however, contraction or relaxation of the iris produces changes in the intra-ocular tension.

In the treatment of glaucoma, eserine may consequently serve to render iridectomy possible, not only by spreading out the iris but also by directly diminishing the pathologically increased tension.

Fig. 10.—Monkey's eye after eserine (Heine).

In connection with the instillation of ½–1 per cent. solutions of physostigmine in the eye, it should be noted that the greater portion of the instilled fluid reaches the nose and mouth through the lachrymal canals, and that it thus may cause a systemic poisoning. This may be prevented by closure of these canals for a time by pressing on them with the finger, a procedure which may be adopted when any medicinal solutions are applied to the eye.

Other Actions of Physostigmine on the Autonomic Nerve-endings.—

The same augmentation of excitability already described as produced by eserine in the oculomotorius mechanism is produced by it in all other autonomic (parasympathetic) nerve-endings, causing augmentation of the excitability of the cardiac vagus (*Winterberg*), of the intestinal vagus, chorda tympani, and N. pelvicus (*Locwi u. Mansfeld*), and also of the nerve-endings in the sweat-glands.

Consequently, with the systemic action of physostigmine there is increased flow of the tears and saliva, increased secretion of the mucous and bronchial glands, profuse sweating, increased contraction of the muscles of the bronchi, stomach, and intestines, vomiting and violent purging, as also spasmodic contractions of the bladder and at times of the uterus, and finally a slowing of the action of the heart. All these effects may be overcome by sufficiently large doses of atropine. Therapeutically we make use only of its actions on the intestine in conditions of atony, tympanites, etc.

Action on Motor Nerves of Striped Muscles.—Further, physostigmine increases the excitability not only of the above-mentioned autonomic nerve-endings but also that of the nerve-endings supplying voluntary muscles. The excitability of these peripheral terminal organs is so increased that previously subliminal stimuli become effective. If the motor nerve-endings have been paralyzed by curare to such a degree that even the very strongest faradic stimulation of the nerve produces no effect, the excitability may be again restored by eserine and then again completely paralyzed by large doses of curare. This explains why curarized animals which are already suffering from asphyxia begin to breathe again after the injection of eserine and are again able to move (see curare, p. 11).

Harnack and *Witkowski*, by investigating the strength of the directly applied induction current necessary to produce contractions of the muscles, have been able to show that the excitability of curarized frog muscles is increased by eserine, and attribute this result to an action on the contractile substances of the muscles. It is possible, however, that this effect may be due to an action on nervous elements lying peripherally to the point at which curare acts, for the direct faradic stimulation of curarized animals probably does not act directly on the muscle-cells themselves or upon these alone, but also on the terminal nervous organs which lie beyond that part of the nerve which is paralyzed by curare (*Herzen, Joteyko*).

Moreover, the physostigmine produces another very striking and theoretically important effect in the striped muscles,—namely, fibrillary or, more correctly, fascicular twitchings which extend over the whole body and resemble violent shivering from cold. This effect must be due to an action on the nervous terminal organs, for, after section of the nerves, these twitchings continue although with diminished intensity, but may no longer be induced in the muscles whose nerves have been divided and have degenerated (*Magnus*). They are not inhibited by curare, but are readily stopped by small doses of atropine (*Rothberger*) and by lime salts (*Loewi*).

These phenomena suggest that autonomic nerve-endings play a rôle

in producing this twitching of the muscles, and that, therefore, besides spinal motor nerves, not only sympathetic vasomotor nerves but also motor autonomic (parasympathetic) fibres supply the voluntary muscles, which last-mentioned nerves play a rôle in the regulation of heat.

It also appears that in these two systems, the autonomic or parasympathetic and the spinal, we are dealing with a reciprocal antagonism between eserine and atropine in one system and eserine and curare in the other, in both of which cases physostigmine is the weaker antagonist. We may understand this by conceiving that eserine and atropine exhibit a tendency to enter into a reversible chemical combination with the same substances in the nerve-endings, these different drugs causing opposite effects on the functions and possessing a chemical affinity for these substances of very different intensity, so that physostigmine, with less affinity for these substances, may be forced out from these combinations by very small quantities of atropine or curare, both of which possess much stronger affinities to it, in a fashion similar to that in which oxygen is forced by carbon monoxide out of its combination with hæmoglobin. It is, however, possible, and in fact more probable, that, at any rate for physostigmine and atropine, in the iris the points at which the action is produced are not the same.

The elements in the iris which are acted upon by eserine disappear with the degeneration of the nerves, which follows destruction of the short ciliary nerves or the ciliary ganglion, but there still remain in the iris certain excitable elements which are not purely muscular in their nature but which seem to consist of a myoneural intermediary substance. This intermediary substance is not susceptible to the action of eserine, but is excited by pilocarpine (see p. 153) so that miosis is induced. Atropine overcomes this action of pilocarpine, and consequently in all probability produces its effects by acting on this intermediary substance (*Anderson*). With moderate atropinization, therefore, a block is formed through which the normal stimulating impulses of the oculomotorius cannot pass, but which is passed by these stimuli when they are increased by the action of eserine. Complete atropinization, however, can prevent this passage of such stimuli to the contractile substance, and it is thus evident that the antagonism between atropine and eserine is not reciprocal in the strict sense.

Actions on Heart and Central Nervous System.—In conclusion it should be mentioned that eserine also produces certain stimulating effects in the cardiac muscle (*Winterberg*), and that the augmentation of the nervous excitability produced by eserine is not limited to the peripheral organs but manifests itself also in certain portions of the brain and cord. The respiration is strengthened and deepened, as a result of an action on the peripheral vagus endings in the lungs (*Bezold* and *Goetz*) and also of a direct stimulation of the medullary respiratory centre (*Rothberger*). The motor cortical centres are also rendered more excitable, an effect which is especially marked in the presence of a tendency to epileptic convulsions (*Harnack u. Witkowski*).

[The fairly wide-spread use of physostigmine in the treatment of tetanus is not justified by our knowledge of its pharmacological actions. On the contrary, all that we know of it forbids its employment in such conditions.—Tr.]

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PILOCARPINE

Pilocarpine acts on the iris and ciliary muscle similarly to physostigmine, causing miosis, spasm of accommodation, and diminution of intra-ocular tension; but all these actions are weaker and less persistent and are produced only by much stronger solutions (4 per cent.) (*Jaarsma*). A difference in their actions which, while not particularly important, is theoretically a fundamental one, is that pilocarpine does not, like eserine, increase the excitability of the nerve-endings, but actually directly stimulates them. The miosis produced by it occurs even after abolition of the central innervation by post-ganglionic section of the oculomotorius and in spite of a persisting antagonistic action of the sympathetic. With the passing off of its visible effects, the latent increased excitability does not remain, as is the case with physostigmine, but in place of it there is a paresis of the oculomotorius nerve-endings, the pupils becoming wide or normal (*Harnack u. Meyer*), the accommodation remaining impaired, and the near point being rendered more distant (*Falchi*). The other actions of pilocarpine on the autonomic terminal nervous organs are also to be considered as due to a direct excitation.

In respect to their actions on the eye and on most of the other autonomically innervated organs, **nicotine**, **muscarine** (*Schultz*), and **choline** (*F. Müller*) resemble pilocarpine, as does **arecoline**, a base obtained from the betel-nut. The hydrobromate of this base, when instilled into the eye in 1 per cent. solution, produces miosis and a passing spasm of the accommodation, which is followed by slight mydriasis (*Marmé, Lavagna, Fröhner*).

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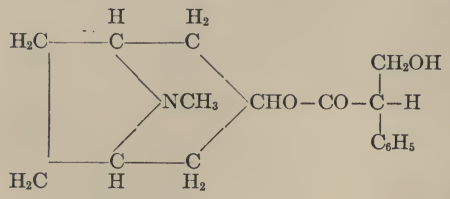
ATROPINE

Atropine and its congeners produce the opposite—*i.e.*, a paralytic—effect on the autonomically innervated organs. This alkaloid, with the empiric formula $C_{17}H_{23}NO_3$, occurs in all the solanaceæ.

In its constitution it is a basic ester, which may be decomposed by alkalies or acids into a basic alcohol, tropine, and an aromatic acid, tropaic acid.

$$\underset{\text{Atropine.}}{C_{17}H_{23}NO_3} + H_2O = \underset{\text{Tropine.}}{C_8H_{15}NO} + \underset{\text{Tropaic acid.}}{COOH.C_8H_8OH.}$$

According to *Willstätter*, its constitution may be represented as follows:



Tropine. Tropaic acid.

For two reasons this formula possesses for us considerable interest. The basic portion, tropine, is closely related to ecgonine (see p. 121); the basic portion of cocaine, which is also an ester and which in many particulars exerts actions similar to those of atropine. As the formula shows, tropaic acid contains an asymmetrical carbon atom, and occurs in three modifications, a lævorotatory, a dextrorotatory, and a racemic inactive one, and forms correspondingly different tropeins. Ordinary atropine is optically inactive, being formed of a mixture of lævorotatory and dextrorotatory bases, of which the former is identical with the natural l-hyoscyamine. This l-hyoscyamine has twice as strong an action on the autonomic nerve-endings as has atropine, a fact which is accounted for by the further fact that r-hyoscyamine is almost without action on these organs (*Cushny*). The closely related alkaloids l- and r-scopolamine exhibit the same remarkable difference in their physiological actions (*Cushny*), and similar differences are noted in connection with other drugs, as, for example, in l- and r-epinephrin. The reason of this different physiological behavior of optical isomeres is unknown.

Mydriatic Action.—If a drop of a 1 per cent. solution of atropine be instilled into the conjunctival sac, after about 15 minutes the pupils commence to dilate, and about the same time the near point moves out, which action continues until the accommodation is completely paralyzed. Both of these actions are due to paralysis of the autonomic oculomotorius nerve-endings in the sphincter of the iris and in the ciliary muscle, for, when the oculomotorius is stimulated inside the skull or the short ciliary nerves are stimulated in the orbit, no effect is produced on the iris of an atropinized eye although the sphincter muscle still reacts well to stimulation (*Schultz*).

In so far as paralysis of the sphincter in all probability increases the tone of the antagonistic dilator, atropine also causes an increase of the tone or of the excitability of the sympathetically innervated dilator. However, this action is neither very apparent nor important, for after even the strongest atropinization it is always possible to dilate the widened pupil still farther by central electrical or peripheral pharmacological stimulation of the sympathetic nerves. When the normal central inhibition of the oculomotorius is abolished, as is the case in sleep (*Rudolph*) or in chloral narcosis (*Levinstein, Ulrich*),

the pupil already dilated by atropine dilates still further. Even this, however, does not indicate that atropine directly stimulates the sympathetic nerve-endings, but only that it depresses the cranial autonomic (parasympathetic) oculomotorius endings.

Duration of the Action.—The effect of atropine in the eye persists for a number of days, the paralysis of accommodation disappearing completely only at the end of 2–3 days, and the mydriasis only after 8–10 days. In old people the effect on the iris is slight, while in presbyopia it is almost nil.

Other Actions in the Eye.—The deceptive micropsia produced by atropine is explained in an analogous fashion to the macropsia produced by eserine. As the wide non-reacting pupil permits the unhindered entrance of bright light, dazzling and photophobia result. Through the retraction of the iris the spaces of Fontana are so distorted that the exit of fluid from the chamber of the eye is hindered, and consequently the *intra-ocular tension is increased,* so that in patients with a disposition to glaucoma an acute attack may be precipitated (see p. 150).

Atropine exerts no action upon the oculomotorius nerve-endings in the iris of birds and reptiles in which the iris is composed of striped muscle-fibres. These nerve-endings, however, are paralyzed by curare, but not by numerous quaternary ammonium bases which in other particulars act like curare, but on the contrary they are strongly stimulated by them. There is, therefore, no essential similarity in the behavior of the striped muscle of the bird's iris and that of the other striped muscles (*H. Meyer*).

Uses in Ophthalmology.—Atropinization of the eye by abolishing the accommodation renders possible the exact determination of the refraction, and, by widening the pupils, facilitates ophthalmoscopic examination of the lens and of the fundus and the performance of operations on the lens, etc. Moreover, the complete quieting of the internal muscles of the eye produces most favorable effects in painful spasm of the accommodation and in all inflammatory conditions such as iritis, etc. This latter action is augmented by a slight anæsthetic action on the sensory nerve-endings of the cornea and iris. For these various reasons, atropine has become one of the drugs most frequently used in ophthalmology. It should, however, be noted that the repeated instillation of atropine into the eye is followed at times by a conjunctivitis and more rarely by œdema of the lids (*Uhthoff*). The cause of this harmful action is not known.

Systemic Actions.—The peripheral action of atropine is exerted on all parasympathetic terminal nervous organs, and consequently, generally speaking, it depresses the motor activity and the tone of smooth muscles as well as the secretory activity of glands. Not only do the mouth and skin become dry as a result of the diminution of the secretions, but the secretion of the gastric and intestinal glands also is diminished. In the heart the inhibitory vagal nerve-endings are paralyzed, so that the heart beats very rapidly and the blood-pressure

rises, while the skin becomes red as a result of the marked dilatation of the small cutaneous vessels and the body temperature rises (*Morat et Doyon*).

Acute Poisoning.—From these various actions arise the characteristic symptoms of acute atropine poisoning, such as is not infrequently observed particularly in children who have eaten belladonna berries. These symptoms are a scarlet-red, dry, hot skin, very rapid breathing and pulse, and dilated pupils, with which are associated active excitement, with delirium, laughing or crying, marked motor activity or even convulsions. As a result of the paralysis of part of the swallowing muscles, there is an inability to swallow. Finally central paralysis develops, causing stupor, an irresistible tendency to sleep, and profound coma that may pass over into death.

Even a few milligrammes of atropine cause in man very pronounced and often violent symptoms of poisoning, but without dangerous results, which latter occur only after decidedly larger doses. The lethal dose for adults is stated to be 0.1 gm., and this is probably too small, but in children 0.01 gm. may cause death.

In addition to the chemical and particularly the pharmacological reactions of atropine, the blue fluorescence of the urine caused by the glucoside scopoletin, which is present in belladonna, as well as in the Scopola japonica, may be of assistance in recognizing and proving poisoning produced by these plants (*A. Paltauf*).

Treatment.—The most essential point in the treatment of atropine poisoning is the thorough washing out of the stomach. If a condition of marked excitement be present, morphine should be administered. In the dangerous comatose stage the various cerebral stimulants, caffeine, strychnine, and camphor, may be administered, and it is probable that free infusion of warm Ringer's solution or of normal saline solution may be of value by helping to dilute and to eliminate the poison. As the bladder is usually paralyzed, it must be emptied by catheter.

Chronic poisoning may result from the long-continued medicinal use of atropine or the related alkaloids, and is characterized by loss of appetite and emaciation (*v. Anrep, Marandon de Montyel*). It is possible that such poisoning is chiefly due to a persistent or at least frequently repeated paralysis of the glandular secretions.

Certain herbivorous animals, particularly goats, sheep, and rabbits, show a very remarkable resistance to atropine. With rabbits this is due to the fact that their blood detoxicates atropine (*Fleischmann*), as does also the liver (*Cloetta*). Horses and cattle are much more susceptible, but dogs of medium size support doses of as much as 1.0 gm. or more, while cats die after receiving a few centigrammes.

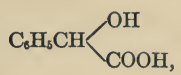
Therapeutic Uses.—In addition to its use in ophthalmology, atropine may be employed for its therapeutic effects in all those conditions in which its actions upon the terminal organs of the autonomic (parasympathetic) nervous system are indicated. For example, for the purpose of inhibiting the secretion of various glands, in profuse sweating, salivation, or lachrymation, in spasmodic conditions of

the organs containing smooth muscles, such as the bronchi, stomach, intestines, gall-bladder, urinary bladder, uterus, etc., or in conditions in which there is an abnormal stimulation of the cardiac vagus. It may also be employed to stimulate the central nervous system, particularly the respiratory centre, as in morphine poisoning (*E. Reichert*).

Preparations.—In addition to atropine sulpate (0.0005–0.001 gm. (!) per dose, 0.003 gm.(!) per diem), various galenic preparations of belladonna, hyoscyamus, etc., are used in medicine. The extracts contain 1–1½ per cent. alkaloids, of which, however l-hyoscyamine makes up the greater portion and atropine the lesser. In hyoscyamus, in addition to hyoscyamine there are small amounts of hyoscine or scopolamine, which accounts for its more pronounced sedative action.

SUBSTITUTES FOR ATROPINE

HOMATROPINE, a synthetically prepared ester of tropine with mandelic acid,



has qualitatively the same pharmacological action as atropine but is much weaker. It is widely employed as a mydriatic, causing a more prompt but less lasting mydriasis than atropine.

SCOPOLAMINE, or HYOSCINE, has also been used as a mydriatic in $^1/_{10}$–$^1/_5$ per cent. solutions, but is more usually employed as a narcotic (see p. 27). It is a tropaic acid ester of scopoline.

Eumydrine.—By the addition of a methyl group the tertiary atropine may be transformed into the quaternary base, methyl atropinum, the nitrate of which has been introduced as a mydriatic under the name eumydrine. In it the general actions on the central nervous system have been markedly weakened while the local effects in the eye are retained (*Lindenmeyer*).

Euphthalmine, $C_{17}H_{25}NO_3$, the hydrochloride of the mandelic acid ester of methylvinyldiacetone-alkamine, is a synthetically prepared alkaloid, which, like atropine, paralyzes the oculomotorius endings, but only in much stronger solutions (5–10 per cent.) (*Treutler*).

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COCAINE

The vasoconstrictors of the eye and the nerves supplying the radial muscles of the iris and the smooth muscles of the lids (Müller's muscle) are derived from the sympathetic system. Their nerve-endings are all stimulated if a solution of cocaine be instilled into the conjunctival sac, but, as cocaine, when thus applied, does not reach the retinal vessels, constriction has been observed only occasionally in cases of general poisoning by cocaine (*Uhthoff*). On the other hand, the vessels of the conjunctiva and the iris are strongly constricted and the pupils dilated while the palpebral opening is somewhat widened. The mydriasis is not maximal and the iris still reacts to light, although to a somewhat limited extent, indicating that the function of the oculomotorius nerve-endings has not been abolished. A further proof that this is so is furnished by the positive effect in the cocainized eye of stimulating this nerve intracranially. Accommodation also remains almost completely normal. Only after long-continued bathing of the eye with a strong (5 per cent.) solution of cocaine is the excitability of the oculomotorius nerve-endings abolished.

If the sympathetic is divided peripherally to the superior cervical ganglion, for a time cocaine still dilates the contracted pupil, but if after a time degeneration of the sympathetic nerve-endings has occurred, cocaine no longer produces any noticeable effects; consequently, it may be concluded that its action is confined to the nervous element only (*Schultz*).

As cocaine paralyzes the sensory trigeminal nerve-endings of the cornea and conjunctiva, it might be thought that the mydriasis produced by it is due to the abolition of sensory stimuli and to a failure of the reflex contractions of the iris dependent thereon. This explanation, however, is shown to be wrong by the fact that other local anæsthetics, such as holocaine, β-eucaine, etc., do not cause any mydriasis.

Effects on Intra-ocular Tension.—As a rule, cocaine diminishes intra-ocular tension, probably on account of its power of constricting the vessels of the ciliary body of the iris, from which the fluid of the aqueous chamber is derived. However, the retraction of the iris by narrowing the canals of Schlemm tends to oppose this diminution of the intra-ocular tension and may, in fact, particularly in patients suffering from glaucoma, at times cause an acute attack of glaucoma (*Uhthoff*).

Uses in the Eye.—Since its introduction by *Koller*, cocaine has come to be a drug which could hardly be spared in ophthalmology, for it very quickly produces a mydriasis lasting only for a few hours, anæsthesia of the cornea and conjunctiva, and anæmia of the ocular tissues. Its value here is somewhat lessened by its liability to damage the cornea, diffuse opacities of the cornea being quite readily caused and the healing of wounds of the cornea being retarded by it.

That the abolition of the function of the sensory trigeminal nerve-endings may be a direct cause of trophic disturbances, if the blood-vessels of the eye be constricted, is demonstrated by the fact that a neuroparalytic keratitis may result

from the simple removal of the Gasserian ganglion, including the vasodilator nerves of the anterior eye which run in the ramus ophthalmicus, but if at the same time the cervical sympathetic and, with it, the vasoconstrictors of the eye are divided, no changes occur in the cornea (*Spallita*). In man, however, because of the consensual closure of the lid, keratitis does not usually occur after one-sided extirpation of the Gasserian ganglion (*Krause*).

Ephedrine and *pseudo-ephedrine* (*Günsburg*), alkaloids prepared from Ephedra vulgaris and *β-tetrahydronaphthylamine* (*Stern*), act on the dilators of the iris and on Müller's muscle similarly to cocaine.

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EPINEPHRIN

Epinephrin and the related synthetic compounds (*Loewi u. Meyer*) act upon those elements of the eye which are innervated from the sympathetic system in the same fashion as does very strong stimulation of the sympathetic nerve (*Wessely*). Fractions of a milligramme injected intravenously cause a very pronounced mydriasis, which, however, lasts but a few seconds, and may even cause a momentary increase in the dilation of a pupil already maximally dilated by atropine (*Lewandowsky*). At the same time the eyeball is protruded and the vessels of the eye are constricted. When instilled into the conjunctival sac in a strength of 1:1000 or even of 1:10,000, epinephrin powerfully constricts the conjunctival vessels, but, as a rule, in man causes no noticeable mydriasis, and also none in dogs and cats, but does so in rabbits and particularly in frogs (*W. H. Schultz, Meltzer u. Auer*). If, however, the sympathetic nerve-endings of the iris are themselves abnormally excitable or are less inhibited by the antagonistic autonomic oculomotorius mechanism than normally, the instillation of epinephrin causes a distinct or pronounced mydriasis. This is the case in man in many cases of Basedow's disease, in which there is an increased excitability of the sympathetic innervation, and also in cases with insufficiency of the pancreas, such as severe diabetes in man, or in dogs and cats in which the pancreas has been extirpated. This pupillary reaction to epinephrin may consequently in certain cases have some diagnostic significance (*Loewi*).

The terminal organs of the sympathetic nerve are also more excitable if they have been separated from their centre, the superior cervical ganglion, and consequently in such case the conjunctival instillation, which is ordinarily without effect, or the subcutaneous injection of epinephrin may cause in rabbits a pronounced and rather lasting mydriasis (*Meltzer* and *Auer*).

The susceptibility of the entire sympathetic motor mechanism to epinephrin may be enormously increased by the administration of cocaine. Doses of cocaine,

which by themselves produce no marked influence on the iris of the cat or dog, so alter the physiological condition of this organ that the instillation of epinephrin causes a pronounced mydriasis. This synergistic effect is still more clearly shown in connection with the action of these two drugs on the sympathetic innervation of the intestine and bladder and on the vasoconstrictors. It is consequently very probable that those actions of cocaine, which we call stimulation of the sympathetic nerve-endings, are essentially due to a specific sensitization of the motor sympathetic nerve-endings for the epinephrin, which is always present in the blood, although normally in subliminal amounts (*Fröhlich u. Loewi*).

Its local vasoconstricting action on the conjunctival vessels and also, when injected subconjunctivally, on the vessels of the iris and ciliary body is very useful in the practice of ophthalmology, particularly when it is used in combination with cocaine.

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Astringent and corrosive substances, or those which cause inflammation, produce the same changes in the outer portions of the eye, the cornea and conjunctiva, as in other mucous membranes; consequently, for their actions on the eye the reader may be referred to the chapter on the pharmacology of inflammation.

Antiseptics.—The same holds true also for the antiseptics, of which the mild insoluble mercury preparations, the yellow oxide and the white precipitate, in the form of ointments, and calomel, in its most finely powdered form, as a dusting powder, are frequently employed in the practice of ophthalmology.

ABRIN

In this section it seems proper to discuss in part the action of abrin, a toxin, probably albuminoid in nature, which is obtained from the seeds of Arus precatorius, or jequirity (*S. Martin, Osborne*). Mere traces of this substance applied to the conjunctiva cause an acute, rapidly progressing conjunctivitis, with emigration of leucocytes and pronounced serous infiltration, effects which at times appear to be of value in the treatment of sluggish trachoma, and particularly as a means of causing the absorption of trachomatous opacities of the cornea. As is the case with many toxins of a proteid nature, an antitoxin—antiabrin—may under the influence of abrin be produced in the organism (*Ehrlich*), and *Römer* states that it is possible to moderate the intensity of a too violent abrin action in the eye by the use of this antitoxin.

DIONIN is another drug causing pronounced conjunctival chemosis and œdema of the lids, which consequently may be used in the same way and for the same indications as abrin. It is the synthetically prepared hydrochloride of ethyl morphine.

PERONIN, the hydrochloride of benzyl morphine, may also be used for similar purposes (*Uhthoff*).

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CHAPTER VI

PHARMACOLOGY OF THE DIGESTION

1. CHEMISTRY OF THE DIGESTION

PHARMACOLOGY OF THE DIGESTIVE GLANDS

SALIVARY SECRETION

INNERVATION.—The chemical transformation of the food starts in the mouth under the influence of the secretions of the salivary glands, particularly the parotid, submaxillary, and sublingual glands, which receive their secretory innervation on the one hand from the superior cervical ganglion of the sympathetic and on the other from

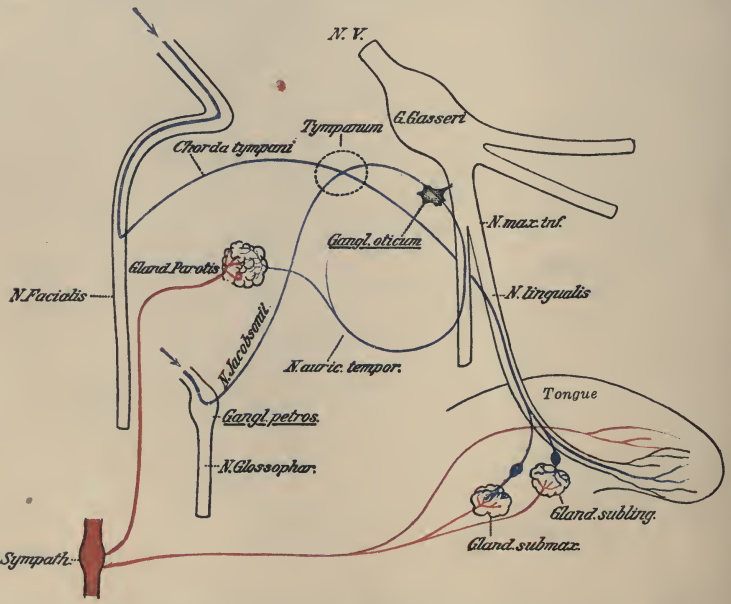

FIG. 11.—Innervation of salivary glands. Red, sympathetic nerves; blue, autonomic nerves.

cranial autonomic nerves. The autonomic fibres for the parotid gland pass from the auriculotemporal branch of the fifth nerve through Jacobson's nerve into the glossopharyngeal, and those for the submaxillary and sublingual glands from the facial nerve through the chorda tympani of the lingual nerve. Both types of nerves also contain vasomotor fibres for these glands, those in the sympathetic being vasoconstrictor while those in the autonomic nerves are vasodilator.

These nerves are, therefore, in this respect antagonistic to each other. The secretory fibres are also in a sense antagonistic, inasmuch as their excitation produces in the glands electric changes of opposite character (*Bayliss* and *Bradford*), and, while in both cases a secretion of saliva results, that resulting from the stimulation of the sympathetic nerves is scanty and viscid * while that following stimulation of the chorda is abundant and thin.

Reflex Excitation.—The salivary secretion may be excited reflexly from the cerebral cortex as a result of stimulation of the appetite, a fact which accounts for the common expression "My mouth waters." It can, however, also be induced by disgust or nausea, for stimulation of the vomiting centre (p. 177) also affects the centres controlling the salivary secretion. This secretion may also be induced by taste, smell, and other sensory stimuli acting upon centres which lie in the subcortical regions and in the medulla. Of these the mechanical stimulus resulting from the act of chewing, which causes an abundant secretion, is especially important.

The parotid gland is much more developed in herbivorous animals, which, as a rule, chew their food for a longer time and more thoroughly, than in the carnivora, who, as a rule, bolt their food, or in those animals which live in the water. In man the average amount of saliva which is secreted is very considerable, amounting under the influence of chewing to as much as 500–700 gm. in an hour, and, as the movements of talking produce a similar effect, in 24 hours as much as 1–2 kilograms may be secreted (*Tuczek*). In the horse and ox the amount secreted in 24 hours may exceed 40 kilograms.

Chemical stimuli, especially acids, bitters, and pungent substances, such as mustard, by their action on the mucous membrane of the mouth, reflexly stimulate all these glands, but especially the submaxillary.

DIRECT STIMULATION

Quantitatively the salivary secretion is directly influenced by:

1. *The composition of the blood,—i.e.,* the water content of the blood and the tissues. If this is very low, as after profuse sweating or diarrhœa, the secretion of saliva stops.

Otherwise the salivary secretion is, within wide limits, independent both of the blood flow through the glands and of the chemical constituents of the blood, it being little influenced even by such substances as the iodides and bromides which are excreted in it. The salts of polybasic acids and sugar are not excreted in the saliva, and metal oxides are excreted only in the form of their halogen salts (*Cl. Bernard*). Herein is seen a fundamental difference in the behavior of the true glands from that of the kidneys.

2. *Substances which excite the extra- or the intra-glandular nervous mechanism.* The cranial autonomic organs are stimulated by these drugs, which in general are autonomic stimulants, pilocarpine, physo-

* In the cat alone the sympathetic saliva is poorer in ash than the chorda saliva (*Langley*).

stigmine, muscarine, choline, acting on the nerve-endings while nicotine stimulates the cells of the ganglia.

Choline, $(CH_3)_3NOH\ C_2H_4O$, is a basic substance which is widely distributed throughout the body (*Fürth u. Schwarz, Schwarz u. Lederer, Kinoshita*) and which forms a part of the complicated molecule of lecithin. It is not improbable that this substance is of considerable importance for the maintenance of the normal tone of the autonomic ganglia and nervous organs, acting upon them perhaps much as does epinephrin on the corresponding sympathetic nervous organs.

The power of TOBACCO, especially when chewed to increase the secretion of saliva, is a matter of common knowledge. Profuse salivation is often a disturbing side-effect of PILOCARPINE when this drug is employed for other purposes, but small doses (up to about 0.04 gm. per diem) are occasionally useful in cases of suppression of the salivary secretion from nervous or other cause, in which the taking of food has consequently been rendered difficult.

MERCURY SALTS may also cause a profuse flow of saliva, a very disturbing and undesirable and by no means infrequent occurrence during mercurial treatment, which is due to an action on the autonomic innervation, but whether centrally or peripherally is not known.

INHIBITION

All these autonomic stimulations of the secretion of saliva may be completely inhibited by ATROPINE and its congeners, although the vessels in the glands are not contracted. As ptyalism—*i.e.*, pathologically augmented flow of saliva due to other causes, such as neuroses, pregnancy, helminthiasis, etc.—as a rule is also primarily due to autonomic stimulation, this symptom may generally be relieved by atropine.

If the secretion of the submaxillary gland be stopped by a dose of atropine just large enough to produce this effect, it may be excited again by pilocarpine and once more stopped by a second dose of atropine. After this larger dose of atropine, however, it is hardly possible again to excite secretion by further administration of pilocarpine. It is thus seen that, while there is a reciprocal antagonism between these two drugs, the affinity of atropine for the autonomic nerve-endings is much stronger than that of pilocarpine, much as is the case with the relative affinities of carbon monoxide and oxygen for hæmoglobin.

Except in very markedly toxic doses, atropine does not affect that secretion of saliva which follows stimulation of the sympathetic. Such may be induced experimentally by the intravenous administration of epinephrin or inhibited by morphine, the effect of the latter being probably due to central action.

The innervation of the other glands in the mouth is essentially similar to that of all the true salivary glands. In them, however, stimulation of the autonomic nerves which reach them through the facial nerve causes a more concentrated secretion while stimulation of the sympathetic nerves supplying them results in a more dilute secretion (*Rethi*), but to drugs they react like the salivary glands.

Elimination through the Salivary Glands.—The chemical composition of the saliva cannot be essentially altered, but with more abundant flow there is a relative decrease of its organic and a relative increase of its inorganic constituents, particularly of the carbonates (*Fleckseder, Binet*). Only a few substances foreign to the body, such as hexamethylenamine (*Hanzlik*) and the iodides, bromides, and mercurial and lead compounds, are excreted by the salivary glands, as are also certain alkaloids, among them morphine and quinine, which, by their bitter taste, betray their presence in the secretion.

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THE GASTRIC SECRETION

Innervation.—The gastric secretion is both excited and inhibited by two sets of fibres which are brought to it in the vagus. While there is no proof that stimuli which can excite secretion reach this organ through the sympathetic nerve, by analogy with the mechanism of the pancreatic secretion, the behavior of which in all other particulars resembles that of the gastric secretion, it may be assumed as probable that they do so.

Chemical Stimulation and Inhibition.—The secretion of the gastric juice is determined normally by the chemical action of the stomach contents on the gastric mucous membrane, quite independently of this nervous mechanism, which is controlled by reflexes acting through the central nervous system, the extractives of meat (meat soup), albumoses, peptones, and bread acting as stimulants, while fats inhibit it. Acids increase while alkalies diminish it.

Even this chemical action on the mucous membrane, however, is also the result of reflexes which occur in the nervous plexuses of the stomach wall and are not affected by section of both vagi. Consequently it may be concluded that they are independent of the central nervous system.

Our knowledge of these and other very important facts concerning the secretion of gastric juice has been obtained by means of the experimental methods of *Pawlow*. This physiologist has devised a method of forming a "small stomach," by separating a portion of the fundus of the stomach from the rest of this organ in such a fashion that it

forms a blind sac opening through the abdominal wall but still remaining connected with the large stomach by nerves and vessels and thus receiving all the nervous impulses which are excited locally in the large stomach or which originate in the central nervous system. The secretory activity of this small stomach gives an essentially true picture of that of the large stomach.

According to *Starling* and *Edkins*, the chemical stimulation of the secretory activity of the stomach is due to the direct stimulation of the gastric glands by secretin, a substance formed in the mucous membrane of the pylorus by acid or by products of digestion.

DIRECT ACTION OF DRUGS

The secretion of gastric juice may be excited by *pilocarpine, choline,* etc., and also by MORPHINE,* and may be temporarily inhibited by ATROPINE. From a practical point of view the action of pilocarpine in conditions of pathologically diminished gastric secretion is of no importance, for the following reasons: Such disturbance of function results either from disease of the gastric mucous membrane (gastritis, carcinoma, etc.), in which stimulation through the vagus would produce no effect and in which only the administration of pepsin and HCl could be of value, or from nervous disturbances (inhibitions), in which case it is often accompanied by a normal or even increased motility and compensatorily increased pancreatic secretion (*Cohnheim*), under which conditions the digestion either remains normal and demands no interference, or else the insufficiently digested ingesta rapidly pass into the intestine and cause diarrhœa, which would only be aggravated by the administration of drugs like pilocarpine, which stimulate the vagus. In such cases assistance is rather to be expected from morphine, which inhibits the motility of the stomach and at the same time, after temporarily inhibiting the gastric secretion, increases it to a considerable extent (see p. 189). [While the above statement is theoretically correct, there is still much in it that is too hypothetical to permit the clinician to adopt such suggestions, particularly as the use of morphine would be extremely dangerous in chronic conditions of subacidity and as the acute cases almost invariably respond satisfactorily to other methods of treatment.—TR.] In this connection it should be mentioned that in chronic morphinism the gastric secretion gradually and progressively diminishes until it fails entirely, re-establishing itself again only if the habit be abandoned (*Hitzig*).

* This has been established by *Riegel* in dogs with a Pawlow small stomach, and also under various conditions in man. On the other hand, *Leubuscher* and *Schafer* found after oral administration of morphine normal acid values but after subcutaneous administration subnormal values. The reason for these contradictory findings is not clear, but it is possible that they are due, at least in part, to the admixture of different amounts of the alkaline saliva (*Bickel u. Pincussohn*).

Reflex Stimulation by Drugs.—A sluggish and insufficient secretion may usually be stimulated in a reflex fashion by substances with a pronounced taste or smell and which stimulate the appetite. Among these may be mentioned wine, salt, spices, and pepper, as also certain substances which even when given by enema produce the same reflex effects by their action on the intestinal mucous membrane. Such are alcohol, ethereal oils (*Wallace* and *Jackson*), and probably many other substances which act as mild local irritants.

Inhibition of Hypersecretion.—Of much greater importance is the relief of the so-called hyperacidity of the gastric juice, which is more correctly, however, a hypersecretion, for, as *Pawlow* has shown, the HCl concentration of the secretion of the peptic glands is never increased above the normal. The apparent hypersecretion, however, is often due to nothing else than an accumulation of the continually secreted gastric juice, which, in cases with motor insufficiency and spasm of the pylorus, is not sufficiently neutralized by saliva from the mouth or by mucus from the stomach (*Katschkowski*). In this connection it should be remembered that hyperacidity itself has a tendency to cause spasm of the pylorus. In such cases the best drugs to use are the *alkaline carbonates, calcined magnesia, lime water, etc.*, which both inhibit the secretion and also neutralize the excess of acid. Lavage of the stomach is also at times indicated in these conditions.

If as the result of motor insufficiency and of the dilatation of the stomach, which usually accompanies insufficiency, the contents of the stomach stagnate, various bacteria may multiply rapidly in the stomach and produce considerable quantities of lactic, butyric, and acetic acid. Under these conditions, although magnesia or soda will neutralize these acids and thus temporarily relieve the acid eructations and heart-burn, their use favors the proliferation of bacteria and thus tends to aggravate the condition. It is, therefore, a better plan to cleanse the stomach by lavage, with or without antiseptics (*Naunyn*). Hypersecretion associated with pyloric spasm, which is frequently present in cases of ulcer of the stomach and which interferes with the healing of the ulcers, may often be relieved by a long-continued use of *atropine,* of which ½ to 2 mg. should be given by needle each day (*Tabora, Schick*).

It may, moreover, be concluded that the secretion of the *gastric juice will be diminished by all substances which mechanically diminish the susceptibility of the gastric mucosa to the chemical stimuli furnished by the food.* Indifferent colloids, like solutions of gum arabic and starch, or fine insoluble powders, such as bismuth subnitrate, talcum, and the like, which adhere to and cover the wall of the stomach, act in this fashion. [It is extremely unlikely that these powders do actually adhere to and cover the wall of the stomach.—Tr.] Whether local anæsthetics, such as cocaine, nirvanin, etc., also indirectly diminish gastric secretion has not yet been determined.

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PANCREATIC SECRETION

As the pancreatic secretion is under the influence of the same autonomic and sympathetic innervation as is that of the stomach, its behavior under the influence of drugs is in most particulars the same as that of the gastric secretion, with the exception that fats cause a stimulation of the pancreatic secretion.

Its secretion may be reflexly excited by stimulating the mucous membrane of the intestine, particularly that of the duodenum, by pungent substances, such as mustard, pepper, and the like; but it may also be excited, independently of other nervous control, by the direct chemical stimulation of the terminal organs (secretory nerve-endings or secretory cells?) (*Gottlieb*). The specific chemical stimulant for this gland is a substance, named secretin by its discoverers, *Sterling* and *Bayliss,* which is formed in the mucous membrane of the small intestine under the influence of hydrochloric acid. Consequently, any hydrochloric acid which passes into the small intestine stimulates the secretion of the pancreatic juice and of bile, while alkalies inhibit them.

That portion of the pancreatic secretion which is excited by secretin is not influenced by *atropine* and *pilocarpine,* but these drugs do influence that portion of this secretion which results from the excitation of the vagal secretory nerve-ending in the pancreas. *This is excited by pilocarpine and choline* * *and inhibited by morphine and by small doses of atropine.* Larger (ten times larger) doses of atropine, however, cause a profuse secretion of pancreatic juice in the dog (*Wertheimer-Lepage, Cohnheim u. Modrakowski*). For this latter effect no satisfactory explanation can be given at present, but it is perhaps due to a depression of the vagal inhibition of the secretion (*Popielski*).

In cases in which *duboisine,* a drug whose action resembles that of atropine, had been used repeatedly as a means of quieting insane patients, it has been observed that the patients lose weight markedly and become ill-nourished, a

* Choline influences the pancreatic secretion in two different ways. Peripherally it excites the vagal secretory nerve-endings and centrally it excites the nerves which inhibit this secretion and which pass to the pancreas in the vagus trunk. It therefore, in small doses, usually inhibits this secretion, and in large doses, after temporarily inhibiting secretion, stimulates it (*Schwarz*).

result which is possibly due to the inhibition of the pancreatic secretion resulting from the use of this drug (*Marandon de Montyel*). As early as 1863, *V. Gräfe* stated that when *atropine* instillations were frequently repeated there resulted a "general irritable weakness and impairment of the power of assimilation."

Internal Secretion.—In addition to the secretion which is poured out into the intestine, the pancreatic gland, in all probability, produces an internal secretion which is carried throughout the body by the blood, and which is of decisive importance in connection with the utilization of the carbohydrates, as well as for the normal absorption of the fats. When this internal secretion fails, as in cases of pathological degeneration or experimental extirpation of the pancreas, severe diabetes develops and, as a rule, the absorption of fat is markedly impaired.* The oral administration of pancreas preparations appears in these cases to improve the absorption of fat, but produces no favorable effects whatever on the diabetes. *Thus far we know of no drugs or other agents which increase or diminish or in any other fashion influence the internal secretion of the pancreas.*

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THE SECRETION OF THE BILE

The secretion of bile is controlled by the same nervous and chemical influences as is that of the pancreas. Under the influence of the ingestion of food these two secretions run along almost exactly parallel (see Fig. 12), both being stimulated by secretin. The expulsion of the bile from the gall-bladder is accelerated by drugs which stimulate the vagus and inhibited by those which stimulate the sympathetic.

Under the influence of *pilocarpine* the gall-bladder contracts and the sphincter of the ductus choledochus closes, but a little later relaxes completely. *Atropine*, on the other hand, causes a relaxation of the gall-bladder and of this sphincter (*Doyon*), an action which is therapeutically of importance in connection with gall-stone colic, which probably is produced by contraction of the bladder and not by that of the duct (*Aschoff*).

* This is not always the case, however, for when the pathological condition develops slowly the absorption of the fat may remain normal or after temporary impairment may become normal again (*Fleckseder, Lombroso*).

Cholagogues.—Of particular importance to the physician is the question whether or not there are any drugs or other means of appreciably increasing the secretion of bile without producing other undesirable effects.

The drugs of the pilocarpine group are not suitable for this purpose, as they affect all the organs of the autonomic system. Further, they simply cause the bile to flow out of the gall-bladder more rapidly without augmenting its secretion by the liver. However, certain substances are known to be *specific stimulants of this secretion.* These are *bile itself or the salts of the biliary acids, soaps, albumoses, dilute HCl (Weinberg) and to a lesser degree the benzoate and the salicylates of soda. Neither soda nor Glauber's salt or other cathartics produce any demonstrable increase in the secretion of bile, while calomel in cathartic doses actually inhibits it* (*Prevost* and *Binet, Doyon* and *Dufourt*).

Gall-stone patients are commonly advised, often with benefit, to use Carlsbad salts or sodium oleate (under various trade names) or various mixtures of cathartics. (One popular one, chologen, contains calomel, podophyllin, and an ethereal oil.) It is difficult to determine whether these drugs are actually curative or not. Probably the benefit which often follows their use is chiefly due to their power of curing or relieving the inflamed and irritable condition of the mucous membrane of the gall-bladder, which renders it tender and causes spasmodic contractions of the gall-bladder, by which gall-stones, which may be present without causing symptoms, are forced into the duct, causing colic and obstructive jaundice. In this connection, it is to be remembered that chronic inflammation of the mucous membrane of the gall-bladder is always a necessary preliminary condition for the production of the gall-stones themselves (*lit., Naunyn, Herter*). It is difficult to imagine in what manner Carlsbad salts can exert any favorable effects on the mucous membrane of the gall-bladder, for probably neither the neutral salts nor the carbonates are excreted in the bile.

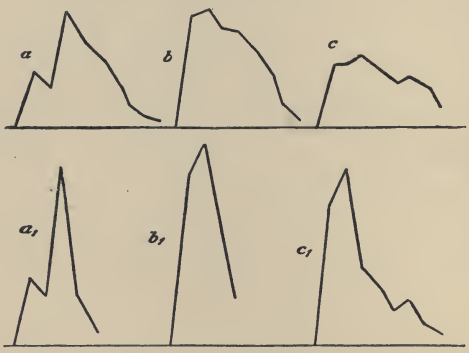

Fig. 12.—Secretion after taking food: *a*, pancreatic secretion after milk; *b*, after meat; *c*, after bread; a_1, gastric secretion after milk; b_1, after meat; c_1, after bread.

Elimination and Antisepsis.—Different drugs and poisons are secreted by the bile, among others Cu, Pb, Hg (*Langer*), amyl alcohol, methylene blue (*Brauer*), menthol (*R. Stern*), and hexamethylenamine (*Crowe*). Of the last two, when administered in sufficient doses (of menthol 6.0 gm., of hexamethylenamine 5.0 gm. per diem), enough is secreted to sterilize the bile.

When the bile is prevented from joining the pancreatic juice in the intestine, this latter cannot by itself properly prepare the fats for absorption, so that the stools contain large amounts of fat. It is quite remarkable that under these conditions the administration of bile with the food is of no benefit. Apparently the pancreatic juice and the bile must be very thoroughly mixed together and in exactly correct proportions in order that this function shall be properly performed, and apparently such a mixing cannot be attained artificially.

Other Liver Functions.—The manufacture of bile is only one of the many functions of the liver, which is an organ in which analytic and synthetic reactions of most varying nature take place. Among these functions one of the most important is that of transforming the carbohydrates into glycogen and storing them up as such, and of forming and supplying glucose to the body as it is needed. How these two chemical processes are controlled is unknown, but it is very probable that the formation of glycogen is accomplished with the aid of the internal secretion of the pancreas, and that the transformation of glycogen into glucose takes place under the influence of epinephrin, the internal secretion of the suprarenals.

Other chemical functions of the liver, such as the anabolism of fats and proteids, are probably markedly influenced by the internal secretion of the thyroid, iodothyrin, but concerning this we know comparatively little. From all that is known, however, it appears that, in contrast to the function of the true glands, the activity of the liver is regulated not by secretory nerve impulses but by chemical stimuli, which are supplied by specific substances, *Starling's* hormones, and also by the composition and amount of the blood supply.

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THE SECRETION OF THE INTESTINAL JUICE

The secretion of the intestinal juice—the chief constituents of which are, in the duodenum, the ferment, enterokinase, which activates trypsin, and, in the jejunum, invertase and erepsin, which possesses the power of decomposing the albumoses—is excited by local, mechanical, or chemical stimulation of the intestinal mucous membrane, par-

ticularly by the pancreatic juice and by the ingesta. Up to the present, the extent to which the central nervous system controls this secretion has not been sufficiently investigated, and the same is true as regards the action of drugs. Consequently, we know little of the manner in which this secretion may be affected by pharmacological agents.

The mucous glands, which are present throughout the whole extent of the alimentary tract, are stimulated to secretion by the alkaline carbonates and are inhibited by acids and astringents. These latter drugs also precipitate and render insoluble proteid substances dissolved or suspended in the fluid contents of the intestine, and consequently they increase the consistency of the intestinal contents and render them drier.

Elimination through the Intestine.—As has already been mentioned in connection with the secretion of saliva and of bile, various substances for which the body has no further use, such as Ca, Fe, phosphoric acid, and organic detritus and various foreign substances, are eliminated in the different digestive juices. It is thus apparent that the mucous membranes of the stomach and intestine are organs of excretion, a fact which is of particular importance in connection with certain poisons. Thus, compounds of the heavy metals, Pb, Cu, Hg, Bi, Fe, and Mn, and arsenic and antimony and the halogen salts of the alkalies, are excreted in this fashion, as are also morphine in considerable extent and, to a less degree, other alkaloids and the drastic cathartics, aloin and podophyllin, as also bacterial toxins and snake venom. The harmful actions on the intestine which result from the administration of many of these substances, even when administered subcutaneously or intravenously, is due to their excretion by this route.

ABSORPTION IN THE ALIMENTARY CANAL

IN THE STOMACH

Absorption occurs throughout the whole intestine, starting in the duodenum and ending in the rectum. With the exception of those substances which are soluble in the lipoids, the mucous membrane of the mouth and of the stomach does not absorb mentionable amounts either of water or of food-stuffs or other substances in aqueous solution (*Karmel, Meltzer*). Lipoid soluble substances readily penetrate the epithelial covering and more or less rapidly enter the blood, so that it is possible that such substances as nicotine or phenol may be quite readily absorbed by the mucous membrane of the mouth in amounts sufficient to cause a systemic poisoning. The slight power of the stomach to absorb substances which are not soluble in the lipoids—for example, most salts of the organic and inorganic bases—may be of pharmacological importance in cases with motor insufficiency of the stomach, as a result of which the gastric contents

remain for many hours in the fundus of the stomach, for under such conditions the expected effects from medicines administered by mouth may not occur or may at least be very markedly retarded. The same result must naturally ensue if the motor activity of the stomach has been inhibited by such drugs as morphine or epinephrin, in which case the gastric contents do not pass on into the duodenum, in which, as already stated, absorption really begins.

Acceleration of Absorption.—If the lipoid structure of the superficial layer of the mucous membrane be loosened or softened, water and salts, sugar, peptones, etc., in solution are able to pass into it more readily, and consequently may be absorbed. This is apparently the explanation for the fact that fluids containing alcohol or carbonic acid and substances dissolved in them are absorbed from the stomach, although only in small quantities (*v. Tappeiner, Hirsch, v. Mering*). According to *Brandl,* pungent irritating substances like oil of mustard or of peppermint, or pepper, increase absorption. As this is not due to the hyperæmia as such, which is caused by them, it must be due to a chemical change in the cells, a cytolytic action, altering their permeability.

Bitters do not directly favor absorption from the stomach, although they cause hyperæmia of the mucous membrane, but when taken an hour before eating it is claimed that they do so (*Jodlbauer*). In dogs large doses, more especially if repeatedly administered during a considerable period, apparently retard the emptying of the stomach and consequently also retard the absorption of the food from the intestine, but small doses apparently accelerate both these processes (*Heubner*).

Retardation of Absorption.—Mucilaginous substances, such as gum arabic, starch, and pectin, markedly diminish the resorptive power of the stomach (*Brandl*).

ABSORPTION IN THE INTESTINE

The intestinal mucous membrane absorbs not only lipoid soluble substances, but also those insoluble in the lipoids yet soluble in water. Most, but not all, of the effective forces to which this absorption is due are known to us, and are diffusion and osmosis on the one hand and filtration pressure on the other. The latter is apparently of subordinate importance, and is furnished partly by the pressure of the muscle of the intestinal wall and partly by the pumping action of the muscles of the villi. Contraction of the intestinal vessels retards, and dilatation accelerates absorption (*Sollmann, Hanzlik* and *Pilcher*). In very general terms it may be stated that lipoid soluble substances are incomparably more readily and rapidly absorbed than those insoluble in the lipoids, and in general in direct proportion to this solubility.

Höber, by his very ingenious experiments, has shown that very probably the path of absorption for substances which are insoluble in lipoids lies between the cells, but for those soluble in lipoids through the cells themselves,

the absorption occurring in the former instance intercellularly, in the latter intracellularly.

It has not been definitely established just how the fats, which are insoluble in water, are absorbed, but it is probable that they are first saponified or else, like the fat in the blood-serum, are rendered soluble by chemical union with lecithin and proteids (*Miescher*). However, recent observations (*W. Croner*) indicate that in the dog a large portion of the fat is absorbed from the small intestine in a state of emulsification and is not first saponified, and that larger portions are absorbed in the lower than in the upper segment, while the absorption of the saponified portion occurs only in the lower segment. After absorption the fats pass into the intestinal lymphatics and mesenteric veins.

Cod-liver oil enjoys a peculiar reputation as a food and as a curative agent. To it have been attributed, partly because of the presence in it of an inconstant and very small amount of iodine or of certain basic substances (*aselline,* etc.), curative properties in tuberculosis, scrofula, rickets, and other diseases. Certainly established in regard to it are the two facts, that it is more readily and permanently emulsified than other fats, a property not due entirely to its containing free fatty acids, and that it, especially before purification, is much better absorbed from the intestine than other fats (*Gad, Marpmann, Naumann, Croner*).

These properties are sufficient to explain its value as a very efficient, because very digestible, means of improving digestion, but are not sufficient to explain its other real or fancied curative properties. As is well known, cod-liver oil, even the official purified oil, has a most repulsive taste, which cannot be entirely corrected by the addition of flavoring agents. Perhaps impregnation with carbonic acid is the best manner of securing this. Lipanin (pure olive oil with 6 per cent. oleic acid), recommended as an agreeably tasting substitute, is utilized much more poorly than cod-liver oil and even than pure olive oil.

The saturated non-volatile hydrocarbons, the paraffins, which can in no way be brought into solution in water, are not absorbed from the alimentary canal.

ABSORPTION OF SALTS

The rate of absorption of the lipoid insoluble substances, such as the inorganic and organic salts, the sugars, amido acids, etc., in general runs parallel with their rate of diffusion. With isotonic and slightly hypertonic solutions of neutral salts, the rate of absorption increases with their anions as follows: $HPO_4 < SO_4 < NO_3 < Br < Cl$, and with their kations, $Mg < Ca < Na < K$, and exactly the same order holds good for their observed rates of diffusion. With the salts of organic acids also the rates of absorption are found to vary proportionately to their diffusibility, but here their lipoid solubility influences their absorbability to some extent (*Höber*).

In general it may be stated that the salts of sodium, potassium, and ammonium with monobasic acids are readily diffusible and absorbable, while those with the polybasic acids diffuse slowly and are also

absorbed with difficulty (*Wallace* and *Cushny*).* The same parallelism holds good in general for non-electrolytes, such as the various sugars and amino-acids, but salts, such as the fluorides or oxalates or the salts of barium, the anions or kations of which are toxic to the intestinal epithelium, behave quite differently, being absorbed much more slowly than would be expected from their diffusibility. The permeability and resorptive power of the intestinal mucous membrane may be very markedly impaired by the toxic action of other substances (*Scanzoni*), but no one has thus far investigated whether this be due to a chemical alteration of the colloid membrane formed by the epithelial lining or to the paralysis of the active physiological factors such as the muscles of the villi. As this can be properly discussed only after discussion of the mechanism of the digestive processes, it will be taken up later, as will the pharmacological significance of absorption in the intestine in the section on cathartics.

As the blood from the whole of the small intestine and of the colon passes through the portal vein into the liver, while the rectum is drained by the hemorrhoidal plexus, from the middle portion of which the blood passes directly into the general circulation, it is not a matter of indifference from which portion of the alimentary canal food or drugs are absorbed. This is the reason why powerful poisons, such as morphine, strychnine, and particularly carbolic acid, when administered by rectum may under certain conditions cause more rapid or pronounced poisoning than when they are introduced into the stomach, in which case they must first pass through the liver and only gradually enter the general circulation, particularly as the poisonous effects of most toxic substances are markedly lessened by passage through the liver, partly as a result of being chemically changed by conjugation with sulphuric acid, etc., and partly as a result of absorption and consequent retarded entrance into the general circulation (see Curare, Potassium Salts, etc., and also *Rothberger u. Winterberg*).

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* These authors have called attention to another parallelism in connection with these substances. The anions of the easily absorbed salts form readily soluble salts with calcium, while those of the salts which are absorbed slowly form insoluble calcium salts. This, however, does not hold good for all cases, for potassium ferrocyanide is slowly absorbed although calcium ferrocyanide is readily soluble in water.

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II. THE MECHANICS OF DIGESTION

DEGLUTITION

The first of these are mastication and deglutition, which latter may be voluntarily inaugurated by pressing the root of the tongue against the palate, but which when once started is reflexly completed even against the will, the peristaltic action of the œsophagus pushing its contents downward and the cardia opening to permit their entrance into the stomach. The chief nervous centre presiding over this act lies in the medulla, and receives its afferent impulses from definite portions of the throat, the so-called swallowing points, which are specifically innervated by sensory nerves derived from the trigeminal, superior laryngeal, and glossopharyngeal nerves, and which are stimulated by contact with fluids or solids.

Pharmacological Interference with Deglutition.—If these points are benumbed by the application of cocaine, such stimulation no longer causes swallowing, an effect which at times may be desirable during operations on the pharynx or larynx. During general anæsthesia or in deep morphine narcosis, this centre becomes so unexcitable that stimulation of it results in swallowing movements only in the muscles of the pharynx but not in those of the œsophagus or cardia (*Meltzer*).* This should be remembered when treating narcotized individuals; for liquids administered to them should not be simply poured into the mouth, but should be introduced into the stomach through the stomach-tube. In general anæsthesia the secretion of saliva should either be suppressed by such drugs as atropine or scopolamine or care should be taken to remove it from the throat, for the abolition of the swallowing reflex leaves the glottis open, so that the saliva may flow into the lungs and cause an inhalation pneumonia.

Deglutition may also be completely or partially prevented by paralysis of the motor nerves in some or all of the muscles of deglutition. Pharmacologically such paralysis may be caused by drugs with a curare action, which paralyze the striped muscle in the upper portion of the œsophagus, or by autonomic paralyzants like atropine, which prevent the action of the smooth muscles of the lower œsophagus

* Am. Journ. of Physiol., 1899, vol. 2, p. 266.

and of the cardia. This is of significance in connection with the symptoms of belladonna poisoning. This action of atropine would also justify its employment to relax œsophageal or cardial spasm.

MOVEMENTS OF THE STOMACH

In the muscular movements of the stomach one may distinguish peristaltic and antiperistaltic movements, which latter occur during vomiting, a discussion of which follows:

Vomiting, like swallowing, is a reflex phenomenon in which numerous smooth and striped muscles coöperate together in an orderly fashion. The pylorus being closed, the contraction of the antrum of the pylorus drives the stomach contents into the fundus, which, previously and independently of its fulness, actively dilates as a result of relaxation of its tone (*Frantzen*). At the same time the cardia opens, so that the spasmodic contraction of the diaphragm, of all the abdominal muscles, and also of the muscles of the fundus, all starting at the same time, expel the stomach contents through the œsophagus and pharynx. The coördination of these various acts is controlled by a centre lying in the medulla, the so-called vomiting or emetic centre.

Emetic Centre.—A region has been discovered by *Thumas* in the lower layers of the medulla below the calamus scriptorius, electric, mechanical, or specific stimulation of which induces vomiting. This appears to be a coördinating centre, under whose influence the centres for the innervation of the cardia and of the stomach, which lie in the caudate nucleus and in the region of the corpora quadrigemina (*Hlasko*), and the reflex centres controlling the abdominal respiratory muscles, which are also involved in vomiting, are excited to a general coördinated action. Elimination of one of these centres—as occurs, for example, if the corpora quadrigemina be destroyed (*Hlasko*), or if the respiratory centre be inhibited by apnœa (*Grimm, Grewe*)—prevents successful vomiting, as does also the prevention of the reflex by which the cardia is opened. According to *Valenti,* the opening of the cardia in vomiting may be brought about only reflexly as a result of the gastric and œsophageal movements, and never directly by central action. The centripetal fibres for this reflex run in the glossopharyngeal and vagus nerves, and may, at least in the dog, be so effectively put out of function by cocainization of the pharynx and upper œsophagus that the stomach is not emptied, in spite of all the other movements of vomiting.

The vomiting centre may be directly stimulated mechanically as by the pressure of tumors or meningeal inflammation, or chemically as in uræmia, or by various drugs or poisons, or by disturbances of the circulation in the brain. It may also be stimulated indirectly or reflexly by various stimuli, among which are psychical ones, such as disgust, or by labyrinthine disturbances, or by irritation of the pharynx or of abdominal organs. The centripetal impulses from the abdominal organs to the medullary vomiting centre pass upward in the vagi, for, after their division, vomiting can no longer be induced by influences acting on the stomach or intestine.

The solipedes, ruminators, rodents, and chiroptera (bats) cannot vomit, as they do not possess the necessary coördinating mechanism. If the pathologically dilated fundus be overfilled, vomiting is generally difficult, but in the less developed fundus of small children it is facilitated, because simple contraction of the antrum of the pylorus unassisted by the pressure of the abdominal muscles is sufficient for the expulsion of the stomach contents because the tone of the cardia is so weak (*Valenti*).

Narcosis of the Emetic Centre.—In deep narcosis, such as that caused by morphine, chloral, etc., the vomiting mechanism does not act (*Harnack*), and consequently under such conditions the emptying of the stomach may often be attained only by the use of the stomach-tube.

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EMETICS

All substances which, by their powerful action on the mucous membrane of the stomach or intestine, cause irritation, inflammation, or corrosion, may cause vomiting. Consequently, vomiting is a very common symptom in almost all poisonings, and thus forms one of the most important reactions by which the organism protects itself. As emetics in the more limited pharmacological sense, however, we speak of and use only substances which cause vomiting as their primary effect without, for the time being, appreciably affecting other organs than those which participate in the act of vomiting. One can differentiate between

1. Direct emetics, which excite the vomiting centre directly, and
2. Reflex emetics, which act by irritating those specific sensory nerve-endings, in the mucous membrane of the stomach and intestine, the excitation of which induces vomiting.

We are forced to assume the presence in the intestinal mucous membrane of specific "emetico-sensory" nerve-endings, because these react to certain stimuli such as marked distention and to certain chemical reagents, but not to other even violent stimuli which cause pain or excite secretion or normal peristaltic movements. As is well known, a similar differentiation is found in the cutaneous nerve-endings through which stimuli are excited.

Vomiting, however induced, is always, except in small children, preceded by a prodromal stage of nausea, which is accompanied by pallor, cold sweats, increased secretion from the salivary glands and from the nasal and bronchial mucous membranes. A feeling of nausea and often marked muscular weakness develops, and at the same time the pulse becomes somewhat weaker and more rapid and the breathing rapid and irregular. As a rule, after the stomach has been emptied and vomiting has ceased, all these symptoms disappear, except that traces of the muscular weakness remain (*Ackermann*). It is thus apparent that stimulation of the vomiting centre, even before it has attained the threshold value for emesis, causes an accompanying excitation of a whole group of phenomena, among which the inhibition of voluntary movement is particularly remarkable, and at times is so extreme that it completely paralyzes and renders apathetic the affected

individual so that his condition resembles that of severe shock (*Harnack*).

The slight degrees of nausea, which express themselves only in augmentation of the secretions and perhaps in a diminution of the tone of the bronchial muscles, are utilized therapeutically to facilitate the expectoration of tenacious mucus from the bronchi. *In this way the emetics in non-emetic doses may act as expectorants* (see p. 343 ff.).

CENTRALLY ACTING OR DIRECT EMETICS

Apomorphine.—The hydrochlorate of apomorphine, a base obtained by allowing mineral acids to act upon morphine (*Mathiesen u. Wright*), when injected subcutaneously in doses of 5–10 mg.,* after 5–10 minutes, causes nausea and vomiting, which is repeated two or three times, after which the patient completely recovers from these symptoms. If larger amounts be administered, the vomiting occurs repeatedly for an hour or longer, and is followed by a condition of moderate weakness and somnolence which usually soon passes off. When taken by mouth, apomorphine acts much less energetically, 10–20 times as large a dose being necessary and the vomiting occurring only after half an hour or even later. From this it may be concluded that the vomiting caused by apomorphine is not induced reflexly from the mucous membrane of the stomach and intestine, but *results from direct action on the vomiting centre* after the drug has been carried there in the blood.

This is in accordance with the fact that even after section of both vagi, in which lie the centripetal nerves running from the stomach and intestine to the vomiting centre, apomorphine causes nausea and coördinated vomiting movements, which, however, on account of the disturbance in the motor innervation of the stomach, do not always actually cause emesis (*Grewe*). There is no ground for the assumption that apomorphine also excites antiperistaltic movements of the stomach by direct excitation of the autonomic centres in or near the stomach. The phenomena observed by *Schütz* in stomachs removed from dogs previously poisoned by apomorphine or other emetics, which have been held to speak for this assumption, are to be looked upon as merely typical reversed peristalsis occurring occasionally, which, even without the influence of any drug, may also be caused by anæmia of the stomach and which were repeatedly observed by *Schütz* himself in the unpoisoned isolated stomach (*Frantzen*).

As has already been mentioned, stimulation of the vomiting centre, even when vomiting does not occur, induces associatively the symptom complex of nausea, and if this centre is directly excited by chemical means—as, for example, by apomorphine—or as a result of cerebral anæmia, it is clear that this associative accompanying nausea may be more pronounced and persistent than when the centre is temporarily excited by reflexes from the stomach or intestine.

* In dogs as small doses as 1.0–2.0 mg. are effective, but in cats 10.0–30.0 mg. must be given, and in many of these animals apomorphine is entirely unable to induce vomiting.

Vomiting entirely fails to occur or is only partially accomplished if one of the coördinating mechanisms involved in the act, perhaps that in the corpora quadrigemina, for some reason fails to act. In such case nausea can persist for a long time and be in the highest degree a source of suffering, and the motor inhibition and helplessness, particularly after large but ineffective doses of apomorphine, may be very alarming. In rather exceptional cases such a condition may persist with unabated severity for some time even after vomiting has occurred (*Harnack*), but in such cases this is not succeeded by other harmful results. Even infants of but a few months old can support without harm injections of ½–1.0 mg. of apomorphine (*Jurasz*). Habituation does not follow its repeated administration, *Siebert* having for 4 weeks injected a dog each day with ½–2.0 mg. of apomorphine, each injection being followed after about three minutes by vomiting. However, many commercial preparations of apomorphine are contaminated by a percentage of chloromorphid, a toxic respiratory depressant, which is probably the explanation for some of the cases of poisoning which have followed the medicinal administration of apomorphine (*Harnack u. Hildebrandt*).

Other Actions.—The vomiting centre and its coördinately controlled central mechanisms form the predilective, but not the only point on which apomorphine acts.

In dogs in large doses (0.06–0.1 gm.), and in cats even in emetic doses (0.02–0.05 gm.), it causes a condition of marked excitement and confusion, with accelerated respiration and active forced movements. In rabbits and guinea-pigs also its administration is followed by great restlessness and timidity and an irresistible tendency to gnawing, and after doses of more than 10 mg. convulsions resulting in death occur. Hogs, which normally can vomit, cannot be caused to vomit by apomorphine, but after the subcutaneous injection of 0.02–0.5 mg. they become highly excited and gnaw and bore in the floor and walls of their pens. Similar remarkable symptoms of excitement, an irresistible desire to lick and gnaw, are also produced by apomorphine in cattle and horses, and even chickens and doves are rendered restless by it and peck continually on the floor and at their own claws but do not vomit (*Feser*).

Other Central Emetics.—Many other substances directly stimulate the vomiting and the respiratory centres in a manner similar to apomorphine. Their actions, however, are not so elective, but extend usually to other functions, and consequently they are not suitable for the isolated induction of emesis. In this group belong *aspidosamine,* an alkaloid of the quebracho bark (*Harnack u. Hoffmann*), and *lobeline,* an alkaloid of Lobelia inflata, which formerly was used as an emetic, but now is used only in small non-emetic and safe doses in the treatment of asthma (see p. 345). Probably *veratrine,* the active principle of Veratrum sabadilla and Veratrum viride, should also be placed in this group, for in addition to many other characteristic actions, particularly on striped muscles, it causes vomiting by a central action. Administered subcutaneously it is a very effective emetic in hogs and for this purpose it is used by veterinarians.

Morphine also, by a probably direct action on the vomiting centre, induces vomiting in dogs and, as a late effect, quite often in man.

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EMETICS ACTING PERIPHERALLY OR REFLEXLY

Ipecac, Radix ipecacuanhæ, contains about 2 per cent. of a mixture of the alkaloids, emetine and cephaëline, and also an acid resembling tannin. While both of these alkaloids are emetics and cephaëline is the more powerful one, only emetine has been exactly studied pharmacologically. It possesses a bitter and irritating taste and violently irritates the mucous membranes, causing in them inflammation with paralysis of the capillaries. Consequently, when administered in sufficient amounts, it causes in animals not only vomiting but also violent and at times bloody diarrhœa resembling that caused by colchicine and arsenical or antimonial compounds, to the effects of which emetine poisoning in many particulars corresponds exactly.

As the emetic effects occur no more rapidly and are not produced by smaller amounts when this drug is injected subcutaneously or intravenously than when it is introduced into the stomach, it may be concluded that it acts reflexly on the gastric mucous membrane. The fact that, even after subcutaneous injection, it reaches the gastric and intestinal mucous membrane is evidenced by the inflammation of the intestinal mucous membrane and by the identification of emetine in the intestinal contents (*D'Ornellas*).

On the other hand, *Thumas* states that a solution of emetine applied directly to the vomiting centre in the medulla quickly induces vomiting, and consequently he looks upon it as an emetic which acts directly on this centre. However, in view of the general irritating effects of emetine, his results permit of more than one interpretation. After elimination of the centripetal vagus fibres, vomiting was not caused by it in *Duckworth's* and *Polichromie's* experiments, while in those of *D'Ornellas* they occurred in some cases but only very late and to a very slight extent.

These observations indicate that it acts reflexly and not directly.

In man 10.0–15.0 mg. of emetine cause nausea and after ½–1 hour vomiting, but, on account of the difficulty with which this drug may be preserved, it is not suitable for general use at the present. As galenic preparations of ipecac contain the emetine only in colloidal combination, they never cause marked irritation of the intestine,* but, as should be expected from their very slow absorption, only persistent nausea, and after a sufficient dose (for adults 1.0–2.0 gm.) vomiting

* [The large doses employed in the treatment of dysentery not infrequently cause considerable irritation of the intestinal mucous membrane, and consequently may aggravate or cause dysenteric symptoms, a fact which should not be forgotten when the drug is employed in such cases, otherwise its administration may at times be continued after it has accomplished the desired effect on the amœbæ.—Tr.]

in the course of ½–1 hour. On account of its slow action, ipecac is not much used as an emetic but chiefly as an expectorant.

In its original home this drug has been employed for centuries not only as an emetic but also as a specific in dysentery, being used for this purpose in the form of a concentrated decoction.* After repeated doses it ceases to cause vomiting and its curative action in the intestine manifests itself. Probably the effective factor in these cases is essentially the astringent ipecacuaha-tannic acid (see Astringents).† Consequently "emetine-free" ipecac preparations have been prepared and recommended for the treatment of dysentery, but it is doubtful whether these possess any advantage over any other preparation containing tannin. [There can be no doubt that such preparations are useless in amœbic dysentery.—Tr.]

Copper sulphate in doses of 0.1–0.2 gm. (maximum dose 1.0 gm.), introduced in dilute solution into the stomach, after a few minutes causes emesis and nausea which last for only a very short time. If the vagi have been divided in animals so that the reflex action through the stomach is prevented, copper sulphate causes no vomiting.

Reputed Toxic Action.—Under ordinary conditions the rapid expulsion of the stomach contents keeps this salt from damaging the mucous membrane to any appreciable extent, but, even if it does pass into the intestine with the stomach contents, it is absorbed very slowly and in very small amounts. Consequently harmful effects due to its action after absorption are unknown, even when for months small doses have been administered daily (*Toussaint, Burget, Lehmann*). The supposed poisonous character of acid foods which have stood in copper vessels is almost certainly not due to their containing salts of copper. For these various reasons copper sulphate may be stated to be a relatively safe drug, which can produce a severe gastro-enteritis only in case exceedingly large doses, amounting to several grammes, be administered at one time, in which case it is also possible that systemic poisoning could result. [The prohibition of copper as a coloring agent for foods is not justifiable from a hygienic standpoint.—Tr.]

In molluscs copper and zinc also occur in considerable amounts as normal organically combined constituents of the protoplasm (*Mendel* and *Bradley*). Plants, too, absorb considerable amounts of copper from soils containing it without disturbance of their growth, and in fact under some conditions apparently with beneficial effects. When copper in the form of copper alkali-albuminate or tartarate, which do not coagulate proteid, is injected subcutaneously or intravenously for the purpose of causing a systemic intoxication, even small amounts

* [In dysentery ipecac is best administered in salol-coated pills, each containing 0.3–4 gm. of the finely powdered root.—Tr.]

†[With the above view of the method of action of ipecac in amœbic dysentery few who have had experience with this disease will agree. The translator, like many others, is convinced that ipecac properly employed is the most effective curative agent that we possess for amœbic dysentery. Recent clinical experiences with emetine hydrochloride administered subcutaneously speak very strongly for the assumption that emetine is the efficient curative agent in such cases.—Tr.]

exert a paralytic action on the central nervous system as well as on the striped muscles, and cause manifold degenerations of the tissues, particularly in those of the kidney, while in larger doses it kills by acute paralysis (*E. Harnack*).

Therapeutically copper sulphate is employed as a rapid and certainly acting emetic, but it is hardly possible for it to cause a persistent enough mild nausea for it to act as an expectorant. At the present time it is not possible to formulate any indications for its administration with the idea of its acting after absorption. *It is, however, of particular value as the antidote in acute phosphorus poisoning* [as it acts not only as an emetic but also as a chemical antidote.—Tr.]

Zinc sulphate has the same emetic action as copper sulphate. The medicinal dose is 1.0 gm. per dose and per diem. The fact that nowadays it is seldom used as an emetic is difficult to understand, particularly as the danger of zinc poisoning is quite as slight as that of copper poisoning. Just as copper is present in preserved vegetables and fruits colored green with copper, considerable amounts of zinc are present in fruits dried in zinc trays, but harmful results due to the use of such dried fruits are unknown. The same is true of the effects of the long-continued administration of non-corrosive zinc compounds, even though zinc is slowly absorbed and stored up in all the organs of the body.

According to *Javillier*, zinc, like iron and manganese, is a regular constituent of vegetable protoplasm. When present in very slight concentration, it stimulates the growth of yeast and also of grains.

Zinc compounds, particularly zinc oxide, were formerly employed as supposedly curative agents in chorea, epilepsy, and other nervous diseases. From the few facts known to us of the manner in which zinc acts, as learned from pathological experiments, it is not possible to form any opinion as to the possibility of zinc's exerting any curative action in such diseases.

Tartar emetic, antimony and potassium tartrate, like all other soluble antimonial compounds, introduced into the stomach or intestine, reflexly causes decided nausea and, as a rule, but not always, vomiting.

Toxic Actions.—At the same time this salt, depending on the length of time that it remains in the alimentary canal, produces a more or less deep and extensive corrosion of the epithelium of the mucous membranes, and thus opens the path for its absorption into the blood and lymph-vessels. Moreover, even when the gastric and intestinal mucous membranes remain uninjured, antimony may be absorbed and cause a systemic poisoning, which in all essential particulars resembles that caused by arsenic. This consists in general paralysis of the capillaries (*Schmiedeberg*), weakening of the heart's action, and extensive exfoliative enteritis, which is due in part to an abnormal transudation into the villi resulting from the paralysis of their capillaries and in

part to the direct cytotoxic effect of the antimony, which is re-excreted through these mucous membranes. In addition there is paralysis of the central nervous system, with increasing apathy and motor paralysis.

These actions render the soluble antimony salts extremely dangerous poisons, which are all the more dangerous because occasionally vomiting fails to occur, so that quite large amounts of antimony may be absorbed. The administration of 0.2 gm. of tartar emetic in solution has more than once caused death in adult human beings (*Taylor*). It should consequently be the rule, in case this drug be used at all as an emetic, that if vomiting does not follow within an hour its administration should be followed by a dose of tannic acid, which renders this poison insoluble in the alimentary canal and thus interferes with its action. In the German and Austrian pharmacopœias, the maximal dose of 0.2 gm. per dose, 0.5 gm. per diem, has been reduced to 0.1 gm. and 0.3 gm.

As an Expectorant.—Tartar emetic is not at all suitable for the purpose of producing simply persistent nausea (expectoration), but if any preparation of antimony is to be used for this indication it should be the insoluble sulphide of antimony Sb_2S_5, only small amounts of which are dissolved by the acids of the stomach.

Externally tartar emetic, applied in concentrated solution or rubbed in as a salve, causes after some time burning and inflammation and the formation of pustules entirely similar to those of variola. Moderately severe dermatitis has occasionally resulted from the wearing of clothes the materials of which contained antimony (*Lehmann u. Göbel*). While formerly much used as a derivative, the use of such salves has been correctly abandoned.

Systemic Actions.—To-day, except in the treatment of psoriasis of long standing (*Boeck u. Danielsen*), hardly ever is use made of the chronic systemic actions of small doses of antimony, which are the same as those of arsenic, expressing themselves in similar alterations of the metabolism, the anabolism and catabolism of the tissues. This is probably due to the fact that they cannot be obtained with so little disturbance as by arsenic, for the soluble arsenical compounds are readily absorbed and consequently do not remain in the alimentary canal long enough to cause any irritation, while the antimony salts are absorbed so slowly that they are very apt to cause nausea and vomiting and even severe damage to the tissues.* In all probability it should be possible with suitable organic antimonial compounds to obtain all the therapeutic effects of arsenic, including the etiotropic ones (see Atoxyl, etc.).

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Emesis as an undesirable side action often results from the spasmodic contractions of the gastric and intestinal muscles caused by poisonous doses of lead, barium, fly-agaric (poisonous mushrooms), and tobacco, as also not infrequently when pilocarpine is administered medicinally. The vomiting which occurs after small doses of morphine almost always in dogs, and not infrequently in man, is probably due not only to a central action (see p. 34) but also to a reflex which is excited by the spasm of the sphincter of the pylorus produced by morphine (*Magnus*) (p. 189).

TREATMENT OF VOMITING

The vomiting caused by morphine may often be prevented or relieved by small doses of atropine (*Guinard*), which diminishes or relieves the spasm of the sphincters of the antrum of the pylorus and of the pylorus itself (*Meltzer* and *Auer*). The vomiting caused by pilocarpine is also relieved by small doses of the antagonistically acting atropine, which, however, to a greater or less degree inhibits the other actions of pilocarpine.

Just as the algesic nerve-endings in the skin, and those in the mucous membranes, the peritoneum, and probably everywhere in the body, may as a result of inflammation become hypersusceptible to an extreme degree, and may in such cases react to stimuli which ordinarily are ineffective, so, too, the specific nerve-endings in the pharynx and in the abdominal organs, through which the vomiting reflex is excited, may also become hyperexcitable when these tissues become inflamed, so that vomiting may occur spontaneously or as the result of any irritation which may be present. Examples of vomiting thus induced are the vomiting in gastritis, gall-stone colic, strangulation of the intestines, etc. In such cases excessive and distressing vomiting may be relieved by lessening the irritation or by narcotizing the irritated regions by means of cocaine, orthoform, etc., or by cold,—for example, by swallowing pieces of ice. When vomiting is due to other causes less well understood,—for example, the hyperemesis of pregnancy, seasickness, etc.,—we must endeavor to relieve it by narcotizing the vomiting centre by large doses of morphine with ½ mg. of scopolamine administered subcutaneously, or by the rectal administration

of chloral and by other similar procedures. Possibly the application of ice to the back of the neck, which is occasionally effective, acts in a similar fashion.

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NORMAL MOVEMENTS OF THE STOMACH

By the normal movements of the stomach solid and liquid foods are churned about in the fundus, in which the hydrochloric acid and much the largest part of the pepsin is secreted, and are permitted to pass gradually in a partially digested condition into the antrum of the pylorus, from which, after further preparation, they are shoved along little by little into the duodenum. This gradual movement of the stomach contents is controlled by three sphincters, the cardia, the sphincter antri pylori, and the sphincter pylori. The first two of these close the fundus off from the œsophagus and from the antrum, so as to permit it to act without interference, while the sphincter of the pylorus sees to it that the properly prepared and acidified chyme passes in properly measured portions into the duodenum, where it is further modified and passed along.

As, like every other ferment reaction, the hydrochloric acid-pepsin digestion is very markedly retarded by dilution with water, a provision is made to prevent the admixture of fluids with the contents of the fundus and to allow them to pass along into the antrum in a sort of muscular trough, which runs along the small curvature above the fundus and its contents (*Kaufmann, Cohnheim*).

When the stomach is filled, active but not very extensive peristaltic movements of the fundus occur, by means of which its contents are brought into contact with the gastric juice as it exudes from the mucous membrane. For the performance of this function the fundus constantly accommodates itself to its contents, dilating reflexly without any increase of tension pressure as it grows fuller, and contracting again as its contents pass into the antrum (*Sick u. Tedesko*), the fundus behaving here similarly to the bladder. If as a result of sudden overfilling of the fundus the pressure within it rises to about 25 cm. of water, the cardia opens so that regurgitation or vomiting may occur (*Kelling*). In the antrum of the pylorus the peristalsis is much more active, and is powerful enough to mix its contents thoroughly and to force it out through the pylorus.

Innervation.—The reflex coördinating mechanism for these peristaltic movements of the stomach is situated in Auerbach's plexus, which receives stimulating impulses through the vagus and inhibitory impulses from the sympathetic. In a similar fashion the function of the pyloric and cardial sphincters is controlled by ganglia supplied by the vagus and the sympathetic (*Openchowski*). Division of both the vagi and the sympathetics is not followed by any essential alteration of the gastric automatism or reflexes, but when the vagi alone are divided the unopposed constant inhibitory effect of the sympathetic causes permanent disturbance of the gastric motor functions (*Cannon*).

The normal muscular movements of the stomach may also be reflexly stimulated or inhibited in a reflex manner by chemical action on the gastric mucous membranes or by a direct action on its motor nervous mechanism.

Such reflexes are excited normally by the food and by the gastric juice, the hydrochloric acid of which furnishes the necessary stimulation for the movements of the stomach (*Edelmann*). Peristalsis is also excited by carbon dioxide, the partial pressure of which in the fasting stomach amounts to 30–50 mm. Hg, but which during digestion may rise to 130–140 mm. Hg (*Schierbeck*). This effect is also produced when beverages containing carbonic acid are drunk or when sodium bicarbonate is administered. Those peristaltic movements of the antrum of the pylorus (by which the food is expelled into the duodenum) and the opening of the pylorus (which coöperates with them) are consequently seen to be dependent on the normal acid reaction of the stomach contents, an alkaline reaction

of the stomach contents leaving the pylorus closed, while too high acidity may cause a persistent pyloric spasm. Otherwise the pyloric peristalsis is governed almost entirely in a reflex fashion by the chemical composition of the duodenal contents, alkalinity exciting the emptying mechanism while acidity or unsaponified fats inhibit it. This explains the so-called indigestibility of greasy or very acid foods such as unripe fruits, which remain for a long time in the stomach, being able to leave it only as rapidly as they are absorbed or neutralized in the small intestine or pass along into the colon.

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INFLUENCE EXERTED BY DRUGS ON GASTRIC MOTILITY

In a reflex fashion the normal peristalsis of the stomach may hardly be affected by drugs, but it is possible that the BITTERS stimulate it (*Batelli, Heubner*).

The more concentrated solutions of NEUTRAL SALTS are, the more do they inhibit the movements of the stomach, and it is found that magnesia compounds and sugar solutions inhibit it to a greater extent than do the sodium salts. This is the reason why only those mineral waters which contain very small amounts of salts are used as table waters, for the more concentrated ones only retard the emptying of the stomach and so cause discomfort. For the same reason, during water-cures the stronger mineral waters should always be taken when fasting and as long as possible before eating. The temperature of the water is also not without importance, for warm drinks are passed along through the stomach more rapidly and cold ones more slowly (*Dapper u. v. Noorden*).

The motor function of the stomach can be influenced in a much more effective fashion by the direct action of "autonomic" drugs.

EXCITATION BY "AUTONOMIC" DRUGS

Poisoning with *pilocarpine, physostigmine,* and *nicotine* causes violent atypical gastric peristalsis and readily causes reflex vomiting.

Choline, $(CH_3)_3NOH\ C_2H_4O$, also augments the vagus tone and gastric peristalsis, but much less strongly than the above-mentioned drugs. *Neurin,* $(CH_3)_3\ NOH\ C_2H_3$, which under some circumstances—for example, under the influence of bacteria (*E. Schmidt*)—is formed from choline, is a powerful excitant of the autonomic organs. As choline is a normal constituent of the body fluids and in some diseases occurs in increased amounts, either choline or the neurin formed from it may possibly be the cause of the increased activity of the movements of the stomach and intestine. It is possible also that during digestion it is produced in larger amounts than during fasting, and that it consequently causes an augmentation of the tone of the vagus, which apparently is necessary during digestion.

In this connection it may be mentioned that a number of other drugs excite gastric and intestinal peristalsis, particularly *ergotin* (*Auer u. Meltzer*) and the *digitalis* glucosides, and that consequently the gastric function may be markedly disturbed by the medicinal use of these drugs.

However, the indication to use such stimulating drugs for the purpose of reviving and augmenting gastric peristalsis does not exist practically, for in simple gastric atony a temporary strengthening of the gastric peristalsis lasting about an hour would hardly be of any benefit, and this is all that such drugs could accomplish. *Strychnine* is often prescribed to increase the tone of the stomach, but there is no experimental evidence that it does so (*Langley* and *Magnus, Paderi*).

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INHIBITION OF GASTRIC MOVEMENTS

Atropine inhibits the contractions of the gastric muscles, and thus may be of therapeutic value in all those conditions in which the indication is to moderate too violent gastric peristalsis or in any inflammatory and painful conditions of the stomach wall. For example, in gastric ulcer there is an indication for quieting the stomach as far as is possible and of relaxing reflex pyloric spasm (*Schick*).

Although small doses (of 1.0–2.0 mg.) by no means paralyze the motor ganglia of the gastric Auerbach's plexus, they do depress or paralyze the vagal motor nerve-endings which are physiologically connected with it (*Auer u. Meltzer*), while the inhibitory sympathetic nerve-endings are paralyzed only by such large doses as are never used in practice. Consequently, the result of the administration of moderate doses is that the inhibitory impulses gain the upper hand and the stomach is quieted, an effect which is the more striking the more pronounced the previous stimulation of the vagus nerve-endings has been,—for example, after administration of pilocarpine or choline.

In those conditions in which the activity of the stomach movements is due to a diminished inhibitory tonus, less effect is to be expected from atropine, and, as epinephrin stimulates the sympathetic nerve-endings which are here inhibitory organs, this drug should be the more effective gastric sedative. However, this is at present only of theoretical importance, for when introduced into the stomach or administered subcutaneously epinephrin is entirely ineffective and even when injected intravenously acts for only a few minutes.

Morphine produces a very peculiar effect on gastric motility. In dogs with duodenal fistula *Hirsch* observed that the emptying of the stomach was markedly retarded by morphine. Using Cannon's X-ray

method, in which the food is mixed with bismuth subnitrate and thus may be rendered visible on the fluoroscope, *Magnus* investigated this phase of its action on dogs and cats. He found that under the influence of a few centigrammes of morphine the food remained in the distended fundus, while the middle portion of the stomach, corresponding with the sphincter of the antrum, remained strongly and persistently contracted. Under these conditions the peristalsis of the pyloric portion remained normal and could be readily seen, but the pylorus itself was also tonically contracted, and when the contents of the stomach finally passed into the antrum this constriction of the pylorus retarded for hours its entrance into the duodenum (see Fig. 13).

As a result, the stomach contents left the stomach not after 2–3 hours, as occurs ordinarily, but only after 8–12–24 hours, and, as may be readily understood, in a condition of more advanced digestion

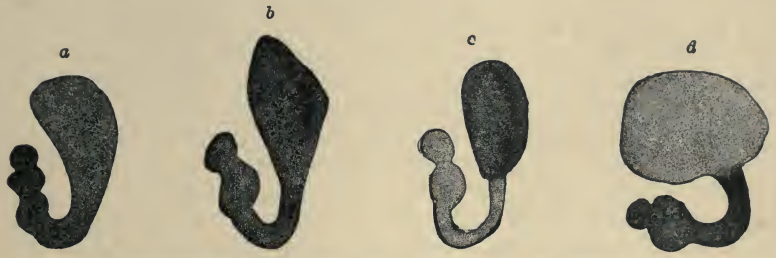

FIG. 13.—Cat's stomach filled with bismuth and potato purée. *a*, before injection of morphine; *b*, 22 minutes after injection of morphine; *c*, 1 hour after injection of morphine, spasm of the sphincter antri pylori; *d*, 3 hours after injection of morphine.

and in a more fluid form than ordinarily. It is clear, however, that, as a result of remaining so long in the fundus, fermentation of the stomach contents may under these conditions occur to a disturbing degree, just as in conditions of motor insufficiency of the stomach due to pathological causes, a fact which should be remembered in treating gastritis, ulcer, and similar conditions. This retardation of the emptying of the stomach by morphine may also affect the rapidity with which drugs are absorbed.

In man these effects on the gastric motility result only from rather larger doses of morphine, amounting to one centigramme or more. Smaller doses, such as 5.0 milligrammes administered subcutaneously or by mouth, usually increase the peristaltic movements of the stomach without causing spasm of the pylorus, and are apt to accelerate the rate at which the stomach is emptied (*v. d. Velden*).

The same accelerating influence of small doses has been observed in dogs, in which at the same time the secretion of the gastric juice is distinctly inhibited, so that the stomach contents reach the duodenum in a less digested and drier condition than normally, but some hours later free secretion of the gastric juice occurs spontaneously (*Cohnheim*).

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THE MOVEMENTS OF THE INTESTINE

The movements of the intestine consist:

First, of interrupted progressive rhythmic contractions of the circular and longitudinal fibres, the so-called pendulum movements, which have for their object the division, mixing, and moving about of the contents of the intestine;

Second, of the true peristalsis, which is excited reflexly by the distention and chemical stimulation caused by the intestinal contents, and in which tonic contraction above the stimulated portion and relaxation below it gradually moves the intestinal contents downward and finally aids in expelling the fæces (*Bayliss* and *Starling*);

Third, violent sudden waves of contraction passing downward over large segments of the small intestine, the so-called rolling movements (*Braam Houkgeest, Cannon, Meltzer* and *Auer*), which force the intestinal contents forward through long stretches of the small intestine, and which, according to *Meltzer* and *Auer*, are exited by a simultaneous augmentation of the vagus tone and weakening of the sympathetic inhibitory impulses.

All these intestinal movements, like those of the stomach, are controlled by the automatic action of Auerbach's plexus, and also by stimulating impulses through the vagus and the hypogastric and inhibiting impulses from the sympathetic through the splanchnic.

PHARMACOLOGICAL ACTIONS ON THE PERIPHERAL AUTONOMIC ORGANS

Consequently, all the intestinal movements, like those of the stomach, may be influenced by autonomic drugs, and may be EXCITED, and, under certain conditions, to such an extent that tonic contraction results, by the action of PILOCARPINE, PHYSOSTIGMINE, etc., on the vagus nerve-endings, while they may be SUPPRESSED by ATROPINE in so far as they are due to excitation produced by vagal impulses. In veterinary medicine pilocarpine and physostigmine are used in colic occurring in horses and cattle, while physostigmine, in the form of subcutaneous injections of ½–1.0 mg. of its salicylate, has recently been employed in human patients for the purpose of securing rapid and complete emptying of the bowels. These autonomic drugs act essentially only on the vagus endings,—that is to say, they act independently of the automatic Auerbach's plexuses and of the sympathetic nervous system.

Auerbach's system, correctly named by *Langley* the "enteric system," acts entirely independently and maintains the automatic and

reflex play of the intestinal movements (*Magnus*). Its stimulation, however, never causes a tonic contraction of the bowel, such as occurs from strong stimulation of the vagus endings, but only a strengthening and acceleration of the contractions. Its ganglia are *stimulated by small doses of atropine and nicotine and also by strychnine* (*Langley* and *Magnus*), and are paralyzed by larger amounts of atropine *and nicotine, which, however, are so large that in man these effects are never observed, not even in poisoning by these drugs.*

PHARMACOLOGICAL ACTIONS ON THE PERIPHERAL SYMPATHETIC ORGANS

All the motor impulses from Auerbach's plexus and from the vagus taken together can, however, be inhibited by strong stimulation of the

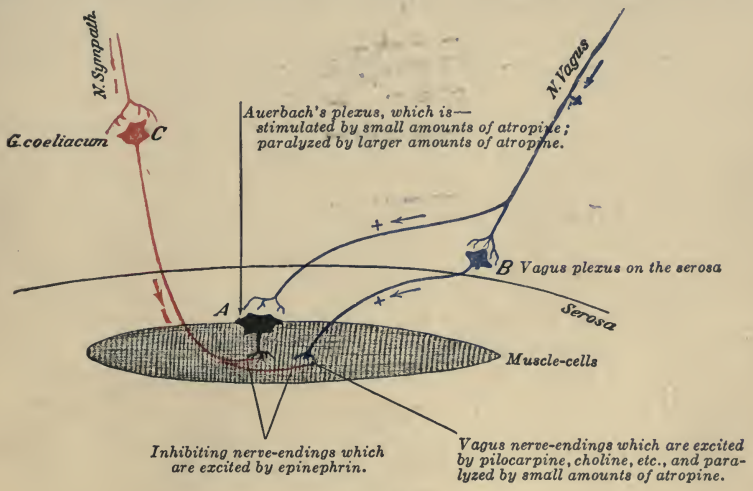

Fig. 14.

sympathetic nerve or of its terminal organs. This may be produced by small doses of NICOTINE, which stimulate the sympathetic ganglia and also temporarily the sympathetic nerve-endings, and can be even more effectively produced by EPINEPHRIN, which, when injected intravenously, acts on the sympathetic inhibitory mechanism in the walls of the intestine and causes their muscles to relax and remain quiet.

Those movements of the intestine which are excited by anything acting directly upon the intestinal musculature independently of any action on its nervous mechanism, are not at all inhibited by atropine and but slightly or not at all by epinephrin. Such probably myogenic excitation may be caused by salts of barium, and somewhat less energetically by poisons of the digitalis group (*Magnus*). However, such pharmacological actions are of no practical significance.

These facts and relationships may be diagramatically indicated as in Fig. 14.

Atropine's pharmacological actions in the intestine are particularly remarkable. These are in part of an opposing or contradictory nature, for through Auerbach's plexus this drug excites motor activity while by benumbing the excitomotor nerve-endings of the vagus it relaxes and quiets them. If to begin with the vagal tone is not considerable, administration of atropine will produce little effect upon it, but in such case it will markedly augment the rhythmic and reflex nervous stimuli originating in Auerbach's plexus, and as a result peristalsis will be actively augmented.

The opposite effect will be produced if at the time of its administration the vagal tone is exerting a strongly preponderating influence, as is the case in cerebral vagus stimulation or in spasm produced by the action of pilocarpine, neurin, etc., in lead poisoning, or in inflammatory irritation. In such conditions atropine, even in small doses, will eliminate the chief factor causing the abnormal tonic contractions, and in this fashion it will cause relaxation and quieting of the intestine.

The above explains the employment of belladonna preparations—0.02–0.05 gm. of the extract by mouth or ½–2.0 mg. of atropine sulphate subcutaneously—on the one hand in a tonic constipation, either alone or combined with cathartics, and on the other hand in spastic constipation, in which a persistent abnormally increased tone of certain portions of the intestines, particularly of the internal sphincter (*Frankl-Hochwart u. Fröhlich*), exists, or in the acute inhibition of all intestinal movement caused by a localized spasm of the intestinal muscle such as occurs in ileus or intussusception.

Morphine, the constipating action of which has long been known, also acts on the intestine at various points. The constipation induced by it is due to several factors, one important one being the persistent closure of the pylorus which has been already mentioned, and which greatly retards the passage of the chyme into the intestine, thus lessening the natural stimulus for peristalsis (*Magnus*), while the temporary inhibition of gastric and pancreatic secretion produces a similar effect (*Cohnheim u. Modrakowski*). In addition, morphine diminishes the excitability of the vagus endings and also of the sensory nerve-endings in the walls of the intestines (*Jacobj, Pohl, Spitzer*) and augments the spinal tone of the inhibitory splanchnic nerve (*Pal u. Berggrün, Spitzer*).

The above experimentally proved statements are, it is true, not generally accepted, but have in no way been contradicted. Recently they have received a certain confirmation by the observation that the violently increased peristalsis in the large and small intestines caused by decoctions of colocynth is visibly quieted by morphine, and even more efficiently by opium, while the accompanying inflammatory transudation of fluid into the intestine is markedly diminished (*Padtberg*). On the other hand, in cats, in which inflammatory irritation of the small intestine was causing abnormally active peristalsis, this quieting effect of morphine could not be observed (*Magnus*).

It is not known whether or not the ileocolic sphincter is, like that of the pylorus, tonically contracted by morphine, but it is probable that this is the case.

From the above it may be seen that under certain conditions morphine may cause the intestine to become entirely or almost entirely quiet. Such a quieting of movements being of essential value in treating inflammatory processes, not only in the intestine but in all organs, it follows that opium is one of the curative agents which could least be spared in acute peritonitis and enteritis. The fact that it has not been possible to observe with the X-ray methods this quieting of the intestine by morphine in no way speaks against its exerting this action, for the effect of the drug depends on the momentary tone and functional capacity of the inhibitory splanchnic centres and nerve-endings, and we do not as yet know how these or the automatic Auerbach's centres behave in an intestine which is inflamed and hyperæmic.* As, furthermore, morphine also inhibits the secretion of the succus entericus, this action will also aid in causing constipation and in quieting peristalsis. It goes without saying that, in addition, the general action of morphine in relieving pain may also be of value in these conditions by calming the patients and softening the reflexly contracted abdominal muscles, etc.

Opium is more efficient than pure morphine when the indication is simply to quiet the stomach and intestine, for the other alkaloids contained in opium also have a constipating but almost no narcotizing action,† so that the desired end may be attained by a smaller ‡ and less narcotic dose of opium than of pure morphine (*Gottlieb u. v. d. Eeckhout*).

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CATHARTICS

Cathartics are medicines which accelerate or bring about the passage of the intestinal contents along the alimentary tract and cause

* See the action in irritation caused by colocynth, p. 192.
† At any rate in cats.
‡ Smaller, that is, in respect to the amount of morphine contained.

emptying of the bowel. The act of defecation is accomplished by the simultaneous peristaltic contraction of the rectum and the opening of the internal sphincter of the anus, while at the same time colonic peristalsis is reflexly excited. It is not exactly known just what normal impulses in the rectum inaugurate the initial reflex for defecation, but probably a certain degree of fulness and of consistency of its contents form the adequate stimulus, although the desire for stool may be present even when the rectum is empty, as in tenesmus, and, on the other hand, may for a long time be lacking in spite of marked and at times in spite of immoderate distention by solid fecal matter. Probably this is due to the fact that the excitability of the rectal reflex mechanism varies greatly under various conditions.

Enemata, etc.—As a rule, defecation may be artificially excited by strong local irritation of the rectum, produced either by mechanical distention with a sufficiently large amount of fluid rapidly injected, or induced chemically by the employment of proper substances. Enemata of water act in the former fashion, the coldness of the fluid augmenting the effect; while various irritating substances act in the latter fashion, for example, solutions of soap or soap cones, enemata of concentrated solutions of salt, or, in an especially convenient manner, a few cubic centimetres of glycerin, which, like the salts, stimulates the nerves in the mucous membrane as a result of its power of attracting water to itself. If the fecal masses in the colon and rectum are very hard, dry, and large, the peristaltic movements of the intestine may prove ineffectual, and in such cases it may be necessary first to render these fecal concretions soft and slippery. This is best accomplished by the gradual introduction, at body temperature and under the lowest possible pressure, through a rubber tube inserted as far as possible into the colon,* of 0.9 per cent. sodium chloride solution containing a little soda, or by injecting olive oil or salve-like paraffin mixtures which are fluid at the body temperature (*Lipowski u. Rhode*). Under these conditions the fluid may be retained for hours and soften the fecal concretions.

Intestinal Colic.—As a rule, stimulation of the intestinal mucous membrane does not cause painful sensation, and consequently chemical or mechanical stimuli acting upon it never directly cause pain. Painful stimuli can, however, originate in the peritoneum when it is markedly stretched or chemically irritated by inflammatory products. Consequently, violent peristalsis of the colon and rectum, when they are filled with solid material, may stretch their peritoneal covering and in this fashion cause pain or colic. In the small intestine, whose contents are always fluid or partially fluid, even active muscular contractions do not readily cause enough distention to produce pain, but only enough to cause a feeling of and the noise resulting from the interrupted and irregular moving about of the intestinal gases.

* [It has been definitely shown that it is impossible, under ordinary conditions, to pass either soft or stiff tubes into the colon.—Tr.]

MANNER IN WHICH CATHARTICS ACT

Cathartic drugs produce their effects either by directly exciting and accelerating the intestinal peristalsis or by indirectly doing so, either by lessening the normal absorption or by increasing the secretion of the intestinal glands and in this way keeping the contents of the intestine fluid and voluminous.

From the character of the stools it is not possible to distinguish sharply between these factors, for on the one hand abnormally active peristalsis does not allow the intestine to concentrate its contents by absorption of the fluid, and on the other the accumulation of abnormally large amounts of fluid in the intestine reflexly excites active peristalsis.

The quantities of fluid which under the influence of the ingested food are poured out into the intestine in the course of the day and which are generally almost completely reabsorbed may amount to as much as several litres.

Bidder and *Schmidt* have estimated them as amounting in the adult man to 9 litres, composed of saliva 1.5 L., bile 1.5 L., gastric juice 6 L., pancreatic juice 0.2 L., and succus intericus 0.2 L.; but here in all probability the gastric juice is estimated at too high a figure. According to newer observations in man, there are excreted in 24 hours: of saliva 700–1000 c.c. or more (*Tuczek, Sommerfeld, Umber*), of bile 600–900 c.c. (*Ranke, Wittich, Hoppe-Seyler*), pancreatic juice 600–800 c.c. (*Pfaff*), gastric juice 1000–2000 c.c. (*Glässner*), in all 3–4½ litres.

From these figures it is evident that even comparatively slight interference with the reabsorption may result in a sufficient quantity of fluid material reaching the rectum to cause a soft or diarrhœal stool. When the absorption is entirely inhibited, as in cholera, continual diarrhœal movements occur, interrupted by short periods of rest, and, as a result, the body loses an enormous amount of fluid and the blood becomes markedly concentrated (*Schmidt*). Under these conditions the fluid material evacuated corresponds exactly in its chemical constitution to normal succus entericus (p. 171).

Essential Properties of Cathartics.—In order for a substance to be suitable for use as a cathartic, it should not act appreciably upon the gastric mucous membrane, but should become active only when it reaches the intestine, where, under the influence of its new environment, it is transformed into a substance which can excite peristalsis or secretory activity. According as this transformation occurs in the small intestine or only after the drug reaches the large gut, it will develop its cathartic action in the small intestine or in the large intestine. In the small intestine the alkaline succus entericus, bile, and pancreatic secretion, with its fat-splitting ferment, are responsible for such transformations, while in the colon they result from chemical reactions, more particularly from reductions due to the activity of putrefactive bacteria.

Under normal conditions putrefaction does not occur in the small gut, but only below the ileocæcal valve, as is evidenced by the presence of H_2S in the large and its absence in the small intestine.

As all cathartic actions are due to reactions taking place on the surface of the intestinal mucous membrane, the efficiency of cathartic drugs will be, at least in part, dependent on the extent to which they are able to act throughout the intestine. From this it may be concluded that cathartics must be absorbed only with difficulty or not at all, and that those acting in the small intestine must pass along through at least the largest portion of it while the others must be able to reach the colon.

From these points of view the cathartics may in general terms be arranged in the following groups:

1. GROUPS INTERFERING WITH THE ABSORPTION THROUGHOUT THE WHOLE INTESTINE.—In this group are included those substances which act osmotically, such as the poorly absorbable salts and sugars and also calomel. According to circumstances and the concentrations administered, they produce their effect in from one to twenty hours and with more or less rumbling of the bowels but without much colic.

2. DRUGS WHOSE CHIEF ACTION IS ON THE MOTOR FUNCTIONS OF THE SMALL INTESTINE.—These include certain oils, colocynthin, and a number of resinous acids, and act in from 2 to 4 hours with more or less rumbling of the bowel but without colic.

3. DRUGS WHICH OWE THEIR EFFECTS ESSENTIALLY TO THEIR ACTION ON THE MOVEMENTS OF THE LARGE INTESTINE.—In this group are sulphur, the anthracene derivatives, and phenolphthalein. They act in about 10–15 hours without causing rumbling of the bowels but often causing colicky pains.

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1. CATHARTICS INTERFERING WITH ABSORPTION

GROUP OF SALINE CATHARTICS

As has already been mentioned, solutions of crystalloids diffusing poorly are in general poorly absorbed (*Höber, Koranyi, Richter*), and, inasmuch as, owing to their power of attracting water, they are able to retain their water of solution and even at times to increase it, they prevent or retard the absorption of the fluid with which they are administered or that resulting from secretion in the small intestine.

Consequently, they cause the accumulation in the intestine of abnormally large amounts of fluid, which pass into the colon and rectum and produce watery fecal discharges. This action is aided and augmented by the increased intestinal secretion which results from the reflex stimulation of the intestinal glands by the concentrated salt solution. In this fashion the sulphates, Na_2SO_4, or Glauber's salts, and $MgSO_4$, or Epsom salts, act as particularly effective cathartics.

This conception of the fashion in which the saline cathartics act, which is based upon the investigations of *Buchheim* and his collaborators, and particularly on those of *Matthew Hay*, finds its proofs in many facts, but particularly in the fact that the fluid bowel movements resulting from the administration of saline cathartics possess the characteristic properties of normal intestinal secretion in both their fermentative properties and their chemical composition, which differs quite as much from that of an inflammatory transudate or exudate as from that of a fluid diluted simply as a result of osmotic diffusion from the tissues. In every particular they correspond very closely to normal succus entericus obtained from intestinal fistulæ, as is shown by the following table:

	Human serum	Acute inflammatory transudate	Chronic peritoneal exudate	Pleural exudate	Normal succus entericus		Diarrhœal stool *Hay*[2]	Cholera stool (*C. Schmidt*)	
					Moreau	*Smith*		I	II
Solids	9.2	8.1	3.0	3.4	1.3	1.1	1.6	1.2	1.5
Organic	7.6	7.2	2.2	2.6	0.4	0.5	0.8	0.3	0.7
Inorganic	1.6	0.9	0.8	0.8	0.9	0.6	0.8	0.9	0.8

Ury has recently investigated in human subjects the action of Apenta water, which contains about 15.5 gm. Na_2SO_4 and 2.0 gm. NaCl per litre, and of solutions of magnesium sulphate, in which he determined the composition of the evacuated fæces. His findings have led him to conclude that large amounts of water are excreted in the intestine by a sort of capillary transudation, for he found these stools to contain very small amounts of ferments, and he therefore concluded that the secretions of the intestinal glands made up but a very small portion of the fluid evacuated. However, it has not yet been determined whether or not these ferments are not in large part weakened or destroyed during their passage through the large intestine (*Grober*), and, moreover, the sodium and chlorine contents of the fluids evacuated, even in *Ury's* experiments, correspond quite closely to that of the normal intestinal secretion.

Various other authors, and comparatively recently *MacCallum*, have assumed that the salines after absorption into the blood stimulate the motor and secretory mechanisms of the intestinal wall and in this fashion cause diarrhœa. However, in contradiction to this view, it has recently once more been definitely shown that intravenous or subcutaneous injections of saline cathartics do not cause diarrhœa, but that when concentrated solutions are used they actually cause persistent constipation, for by causing an increased diuresis they dehydrate the blood and tissues quite markedly (*Frankl, Auer*). However, if very large amounts of dilute salt solutions be administered subcutaneously, so large a portion of this may be excreted into the intestine that it excites diarrhœa, just as it does when administered internally. Further, if a concentrated salt solution be injected under the skin of the abdomen, it, like other irritating substances, may cause a more or less violent local irritation, which may reflexly cause hyperæmia and stimulation of the intestines innervated from the same segment of the spinal cord, and in this fashion cause a diarrhœa

(*Hay*). From other portions of the skin, however, this reflex cannot be obtained.

MacCallum's assumption was based on the observation that intravenous injections of very small amounts of Glauber's or Epsom salts, or the painting of an exposed loop of the intestine with such solutions, excited a muscular contraction of the gut and a secretion by the mucous membrane. While it is true that this effect may be regularly obtained by the local application of such solutions, intravenous injections are only occasionally followed by such effect, and, even when it does occur, the motor stimulation lasts only a few seconds, or at the most a few minutes, and exerts no appreciable influence on the transportation downward of the intestinal contents or their evacuation (*Frankl*). *Padtberg* has also recently confirmed the correctness of *Buchheim's* views.

In another indirect connection, however, *MacCallum's* belief in the specific chemical activity of the saline cathartics finds a support and basis. As already mentioned (see foot-note, p. 175), *Wallace* and *Cushny* have looked upon the calcium-precipitating power of the salines as one of the causal factors in their cathartic action, and it is a fact that the intestinal wall is deprived * of its calcium by those anions which precipitate calcium, among which is the anion which is formed from castor oil. This removal of calcium probably augments quite generally the effect of motor and secretory stimuli (*J. Loeb, Chiari u. Fröhlich*).

The concentration of the saline solutions exerts an important influence on their behavior and their effects in the intestine, for the following reasons. High concentrations (for Na_2SO_4 10–25 per cent.) combine with and hold fast large amounts of the gradually secreted gastric juice, and continue to do this until the salt concentration has sunk to about 3 per cent. When this dilution has been attained, the solution has lost its power of combining with the water or, what in this case means almost the same thing, has lost the power of preventing absorption, and in fact a portion of such a diluted solution is absorbed and enters the blood, although by far the larger portion leaves the intestine in the watery stools. As the dilution of the saline solution—that is to say, the augmentation of the amount of fluid in the intestine—results practically only from the gradual secretion of the digestive juices, it may take many hours before the quantity becomes large enough to produce a diarrhœal evacuation. For example, after the administration of the dry salt to a dog, defecation occurs only after about 25 hours, and, after the administration of a 20 per cent. solution to man, only after 16 hours. Moreover, catharsis is produced by salts thus administered only if the intestine is able to furnish a sufficiently large amount of secretions, and this is dependent on the amount of water present in the blood and in the tissues. If the dog has received no fluid and only dry food for one or two days, the secretions of the alimentary tract are so scanty that a concentrated solution of Glauber's salt may be administered without producing any catharsis.

If, on the other hand, a diluted (5 per cent. or less) solution be administered, it does not retain the fluid secreted by the digestive

* The calcium is in part actually removed and in part precipitated in insoluble form in the tissues forming the intestinal wall. Calomel also produces a similar diminution of the calcium content of the intestinal walls.

organs, and consequently does not increase in amount, but in fact is somewhat diminished, because a portion of the dilute solution undergoes absorption. If the amount administered was by itself large enough, the unabsorbed portion passes rapidly into the colon and causes a diarrhœal stool, which may consequently occur very soon, in 1–2 hours, and which is quite uninfluenced by the water content of the blood and tissues.

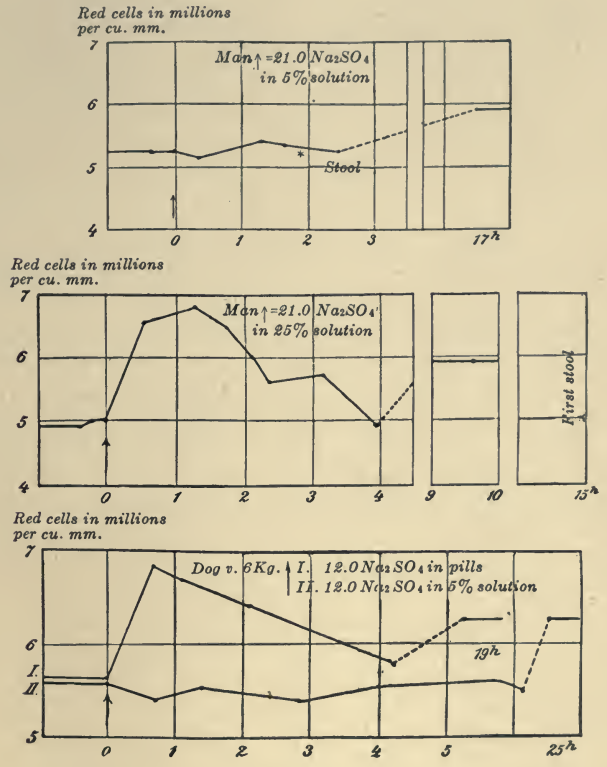

FIG. 15.

It is thus seen that the effect of concentrated and dilute solutions is quite different. After administration of a laxative dose, for example 20 gm. Na_2SO_4, in concentrated solution, a diarrhœal evacuation follows in 10–20 hours and water is removed from the body, but after administration of a small dose in dilute solution,—*e.g.*, 5 per cent., that is to say in a large amount of water,—diarrhœa follows in 1–2 hours, and the water content of the body is not affected. These effects may be readily demonstrated by determining the red-cell content of the blood before and after the administration of the salts (see Fig. 15).

In both cases there may be noted a temporary slight increase in the concentration of the blood, which occurs very late. This is explained by the fact that a certain amount of the salt is absorbed and circulates around in the blood or is stored up in the tissues, which later, when excreted through the kidneys, carries with its solvent water which is thus lost by the blood.

From these facts one may draw the conclusion, that, in those cases in which saline cathartics are to be given for a considerable period in order to exert curative action on the intestinal mucous membrane, they should be administered in dilute solutions, such as the natural cathartic mineral waters, and that, when they are employed to produce dehydration, as in dropsy, they should be given only in concentrated solution. Magnesium sulphate (*Hay*), which is soluble in an equal weight of water, and calcined magnesia in substance are the best drugs to meet this indication.

Hay's investigations also brought to light another important fact,—namely, that, along with its purgative action, magnesium sulphate causes the body to lose a certain amount of its alkali. This is due to the fact that, as this salt is in part decomposed by the carbonic acid in the intestine, considerable amounts of sulphuric acid are absorbed, which are later excreted in the urine, combined with soda and ammonia which is derived from the body. Quantitative determination of the sulphuric acid and the magnesium excreted in the urine under such conditions shows that the sulphuric acid excreted in the urine is sufficient to neutralize about ten times the amount of magnesium excreted. It is thus clear that with the continued administration of this salt the body will lose more or less alkali. This it is able to support for a time by utilizing ammonia for the neutralization of the excess of sulphuric acid, but it is not impossible that when Epsom salts are persistently taken the organism may suffer some damage as a result of such constant loss of alkali, and in practice it is the custom, when using saline cathartics for long periods of time, almost always to employ them in mixtures containing alkaline carbonates, such as are present in the natural spring waters of Carlsbad, Marienbad, etc.

Effects on Utilization of Food.—Inasmuch as the small intestine usually contains, in addition to the digestive juices, more or less food, an accelerated emptying of the bowel and an interference with the absorption must exert an unfavorable effect upon the utilization of the food ingested. According to the analyses available, it is especially the utilization of fats which suffers, this being due not only to the cathartic action of the magnesium salts but also to the fact that the fatty acids and magnesia form insoluble and consequently unabsorbable soaps. While this interference with the utilization of food is not very great, it is an accessory factor in the reduction of weight obtained by the use of various salines.

Effect on Intestinal Flora.—Finally, among the effects of the thorough evacuation and flushing of the intestine by cathartics, mention should be made of their power of removing from it bacteria and their decomposition products, for it is quite possible that numerous symptoms of disease are due to the absorption of toxic substances from the intestine, which give rise to the so-called auto-intoxication. As all attempts to accomplish disinfection, not to speak of sterilization,

of the intestine by the administration of disinfectants have proved unavailing (*Stern*), the most efficient means of removing pathogenic micro-organisms is repeated catharsis. Calomel appears to be the cathartic best adapted for this indication, as its cathartic action starts in the small intestine and extends throughout the whole length of the bowel, and at the same time it possesses some bactericidal powers.*

Effects on the Liver.—It is possible that such cleansing of the intestine plays an important rôle in the treatment of diseases of the liver and of chronic intestinal catarrhs by Carlsbad or other saline waters. It appears not improbable that under such conditions the increased blood-flow through the vessels of the intestine and of the liver, as also the local salt action of the sodium sulphate and the soda, which are absorbed into the blood and lymph, may also play an important part in producing curative effects. The favorable effect of the saline cathartics in diabetes mellitus is much more difficult, in fact practically impossible, to explain.

This increased blood flow through the whole portal system resulting from the action of the cathartics necessarily causes a correspondingly diminished blood flow in other organs, such as the lungs, heart, etc. This has been spoken of as determination to the intestine, and is often employed as a curative or symptomatically favorable action in hyperæmia of the brain or of the thoracic organs.

The chief drugs of this group used in practice are as follows: the sulphates of the alkalies, particularly GLAUBER'S SALT or SODIUM SULPHATE, $Na_2SO_4 + 10H_2O$, or $+ 1H_2O$, containing according to the amount of its water of crystallization 44 or 88 per cent. sodium sulphate, and EPSOM SALT, or MAGNESIUM SULPHATE, $MgSO_4 + 7H_2O$, containing about 50 per cent. magnesium sulphate. These two salts, in doses of 15–30 gm. taken at one time or at short intervals, are efficient laxatives.

All the sulphates if they remain long in the large intestine undergo a reduction, with production of hydrogen sulphide, an effect which occasionally leads to disagreeable borborygmus and flatulence.

As Antidotes.—As sulphuric acid forms insoluble salts with barium and lead, the soluble sulphates may serve as chemical antidotes in lead or barium poisoning. Many toxic substances, particularly the phenols, are conjugated in the organism with sulphuric acid from non-toxic compounds, and consequently it has been believed that in carbolic acid poisoning it was possible to facilitate or augment the distoxication of the absorbed carbolic acid by administering the sulphates. However, neither clinical experience nor laboratory experiments furnish evidence that such is the case (*Tauber*).

Sodium sulphate is the most important ingredient of the waters of Marienbad, Carlsbad, and Tarasp, while magnesium sulphate is the most important ingredient of numerous so-called bitter waters, among

* [More recent careful investigation of the disinfectant action of calomel in the intestine would indicate that it possesses none, or at least none of practical value. See Harris, Jour. of A. M. A., 1912.—TR.]

which may be mentioned those of Friedrichshall, Mergentheim, Apenta, Hunyadi Janos, etc. Artificial Carlsbad salts are a mixture of salts corresponding approximately to the residue obtained by evaporating Carlsbad water and contain about 44 per cent. $Na_2SO_4 + 1H_2O$; 6.0 gm. of these artificial salts in one litre of water roughly represent the natural Carlsbad water. Magnesium sulphate is partially decomposed in the intestine by the carbonates of the intestinal secretions, and bicarbonate of magnesium is formed, which possesses the same power of attracting water and of causing catharsis as does the original salt. When this occurs, the sulphuric acid is in large part eliminated in the urine, temporarily increasing its acidity (*Hay*) (see p. 200).

CALCINED MAGNESIA OR MAGNESIA USTA, although almost entirely insoluble, is transformed in the intestine into the bicarbonate and thus acts as a cathartic. On account of its freedom from taste or other harmful actions, this drug may be readily administered to susceptible patients or to small children, and may also be used with advantage to neutralize acids in the stomach and the intestine, or in poisoning by metallic salts, to precipitate the metallic oxides out of their solutions or more or less absorbable compounds, and in this fashion to render them harmless, at least for a time.

As Antidote for Arsenic.—With arsenous acid magnesia forms a very insoluble salt, and consequently it is commonly used, usually in combination with iron hydroxide, as an antidote in arsenical poisoning. However, experiments on animals poisoned with lethal doses of arsenic have indicated the uselessness of this treatment (*de Bucher*).

Toxic Action of Magnesium.—If absorbed into the circulation, magnesium salts are very poisonous, even a few decigrammes administered intravenously to large animals being sufficient to paralyze the respiratory centre. When following subcutaneous injection the toxic action develops gradually, the respiratory paralysis is preceded by a complete narcosis of the central nervous system, which after 0.8–0.9 gm. $MgCl_2$ per kilogramme of body weight lasts some hours, and then gradually disappears as the salt is excreted. Intravenous injection of calcium salts overcomes this narcosis almost instantaneously (*Meltzer u. Auer*). Lower animals also are narcotized and paralyzed without primary stimulation by salts of magnesia, a fact which is well known to zoologists and utilized by them for the fixation of animal organisms in natural free positions (*Lee* and *P. Mayer*).

[*Boos* has called attention to the very real danger of serious or fatal poisoning from the absorption of magnesium sulphate which has been given to induce catharsis and which has failed to act. The translator is convinced that he has seen evidence of such toxic actions, particularly in cases of postoperative ileus. As sodium sulphate is equally efficient and quite harmless, it should be given the preference in any cases in which there is possibility of intestinal obstruction or paresis.—TR.]

Among OTHER SALINE CATHARTICS are *sodium phosphate*, $Na_2HPO_4 + 12H_2O$, containing 40 per cent. of the salt, used in dosage of 20–40 gm.; the rather insoluble *potassium bitartrate*, $KHC_4H_4O_6$, used in dosage of 5.0–10.0 gm., the readily soluble *Seignette salt*,

potassium and sodium tartrate, $KNaC_4H_4O_6, + 4H_2O$, dose 15.0–30.0 gm., and also the citrates of the alkalies. *Tamarind,* containing large amounts of organic acids, and *mannite* also produce their laxative action in a similar fashion.

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CALOMEL

Calomel, the mild chloride of mercury, mercurous chloride $\begin{pmatrix}Hg—Cl\\Hg—Cl\end{pmatrix}$, should also be considered here.

It occurs in the form of a tasteless white powder, consisting of microscopic crystals which are insoluble in water. By the rapid cooling of its vapor, it may be obtained as a very fine, almost entirely amorphous powder. The name calomel was given on account of the beautiful black color produced by treating calomel with ammonia, according to the formula $\begin{matrix}HgCl\\HgCl\end{matrix} + 2NH_3 = Hg(NH_2Cl)_2 + Hg$.

By contact with the tissue fluids, calomel is transformed into soluble mercuric compounds, probably albuminates, which, without causing an acute local toxic action, are absorbed, and produce a mercurial action which develops very gradually. In the mucous membrane of the mouth and intestine, this action causes a stimulation of glandular secretions and inhibition of absorption, so that under proper conditions it causes salivation and the accumulation of large amounts of fluid in the intestine, with the evacuation of watery stools.

Mercurial salivation may be suppressed by atropine, as may also the diarrhœa caused by it. The actions on the salivary glands appear to be due to a specific pilocarpine-like stimulation of their secretory nerves.

Calomel stools often have a grayish-green color, which is ordinarily attributed to biliverdin, which is supposed to escape the usual reduction to biliprasin on account of the disinfecting influence of calomel. However, *Doyon* and *Eufort* found that calomel produced the same green-colored stools even when the bile-duct is divided and the bile is permitted to escape through a fistula. Consequently, this green color is due to the presence of the sulphide of mercury.

Effect on the Biliary Secretion.—*The bile becomes more concentrated,* and is consequently *secreted more slowly,* as a result of the dehydration which results from catharsis with calomel (*Doyon* and *Bufort*).*

Inasmuch as the first action of calomel is limited to its specific effect on secretion and absorption, and as it causes no irritation or inflammation, but, on the contrary, by its disinfecting action combats to a certain extent the harmful bacteria flora [? see p. 201.—Tr.], calomel may be used without fear in moderate doses (0.05–0.3 gm.) in adults, even in the presence of diseased or delicate intestines, and also in small children (0.01 gm. for infants) and in pregnant women. As a rule, painless catharsis results from its administration.

In order that calomel may act without doing harm, however, it must be rapidly and completely eliminated by the bowel. In the presence of a constipation due to intestinal paresis from peritonitis or to obstruction of the bowel, calomel is a dangerous drug, for under these conditions it will, little by little, go completely into solution and be absorbed, and cause the same symptoms of poisoning as does corrosive sublimate. Further, the administration of calomel to patients taking iodides should be avoided, for, when these two substances meet each other in the tissues, the caustic mercuric iodide is formed.

Diuretic Effects.—The augmentation of diuresis occurring 24–36 hours after the administration of calomel is probably dependent on the fact that calomel causes the accumulation of large quantities of fluid in the intestine, and the fact that, if this fluid is not rapidly enough evacuated from the large intestine, a large portion of it will be reabsorbed from the colon and will cause hydræmia and resulting diuresis (unpublished experiments). This diuresis occurs the more rapidly and to a greater extent the more rapidly the blood is able to replace from the tissues the water lost as the result of the secretion into the small intestine (and this is especially the case in the presence of a general anasarca), for then the fluid absorbed from the colon is added to the blood and causes a marked hydræmia. Moreover, this general effect is the greater, the more slowly the colon is emptied by defecation. Clinical experience has taught us that calomel causes a marked diuresis where these various essential conditions are present,—*i.e.*, in cases with general anasarca and functionally capable kidneys, and especially when the calomel has been given together with opium, which either retards the evacuation of the bowels or entirely prevents it.

On the kidney itself, it appears that calomel, to the extent to which

* Arch. de Physiol. norm. et path., 1897, vol. 9, p. 562.

it is absorbed in soluble modifications, does not act differently than bichloride of mercury and many other metallic salts, in very small amounts causing hyperæmia and irritation and in large amounts producing serious damage. In the presence of nephritis it should, therefore, not be given (see chapter on Diuresis, p. 356). [Many will disagree with this sweeping statement.—Tr.] All the other slowly developing actions of calomel administered internally or subcutaneously and intramuscularly are the same as those of other mercurial compounds. For further details the reader is referred to the chapter on etiotropic drugs.

II. CATHARTICS ACTING CHIEFLY ON THE SMALL INTESTINE

Neutral fats are passed through the stomach without undergoing appreciable decomposition, but are saponified in the small intestine. The soaps formed from the animal and most of the vegetable fats act as very mild irritants to the intestinal mucous membrane, accelerating peristalsis only when administered in considerable amounts. In this fashion 20–30 gm. butter taken on a fasting stomach may produce a mild laxative effect. However, the soap formed from castor oil in the intestine acts as a specific excitant of the peristalsis of the small intestine.

Oleum ricini, or castor oil, is obtained by crushing the castor-oil bean, and by repeated filtration is freed from various impurities,—among others, from the poisonous proteid ricin. It has a flat, repulsive taste, and in many individuals causes nausea, probably because it is decomposed, although only to a small extent, in the stomach. Its irritant action in the small intestine is not intense, and never enough to cause inflammatory irritation, chiefly because these ricinus soaps are absorbed in the small intestine, so that their action is not persistent. In spite of this, however, a sufficiently powerful effect on the peristalsis is usually produced, for it acts on a very large portion of the intestine, as it passes along the gut very gradually and is only gradually saponified (*H. Meyer*). Doses of 15.0–30.0 gm. are followed after 6–10 hours by one or two soft stools without colic. Castor oil hardly ever reaches the large intestine, and consequently produces no effect upon it (*Magnus*). It may, therefore, without fear be prescribed for pregnant women.

Croton oil, oleum crotonis, obtained from the seeds of Croton tiglium, contains crotonoleic acid, partly in a free state, and other unknown substances. Consequently, wherever applied, this drug causes violent irritation and inflammation. In doses of 5.0–20.0 mg. (maximal dose, 0.05 gm. per dose) it acts as a drastic purgative. When purified by alcohol, croton oil is neutral in reaction, tasteless, and unirritating, but, owing to its saponification in the intestine, even this in doses of 0.05 gm. causes violent diarrhœa (*Buchheim u. Krich*).

Certain resinous acids appear to act similarly to ricinoleic acid. Among these are the resins present in the tuberous root of Ipomœa jalapa (**Jalap**) and in the root of Convolvulus scammonia (**Scammony**) and many others. These are all acid anhydrides of a glucosidal nature, which are insoluble in water, but which after reaching the intestine are transformed by the alkaline secretions, particularly by the bile, into soluble and active substances. They then excite violent peristalsis of the small intestine and perhaps also increase secretion, and consequently the intestinal contents are rapidly forced along into the colon. As, however, these resins are absorbed or destroyed only after they reach the large intestine, they cause increased peristalsis here also, with colic and a resulting hyperæmia and reflex stimulation of the other pelvic organs. Consequently, they are by no means so harmless as castor oil.

In this class belongs the fruit of Citrullus colocynthis, the active principle of which is the exceedingly bitter glucoside **colocynthin**, which is soluble in water, and which in small doses, 1.0–5.0 (!) cg. of the extract per dose, causes increased secretion or outpouring of fluid into the small intestine and probably also in the large intestine, and accelerates the peristalsis, while in large doses it causes vomiting and violent inflammation of the mucous membrane of the stomach and intestine (see p. 192).

Similar to this is **gamboge**, a gum resin obtained from Garcinia hanburii, which, in addition to gum, contains as its active principle an acid which in small doses causes a watery, painless diarrhœa, and in large doses colic and gastro-enteritis, and at times abortion.

Finally, mention should be made of **podophyllin**, a resin obtained from Podophyllum peltatum, the active principle of which is a crystalline podophyllotoxin, which is soluble with difficulty in water. It is used in chronic constipation in doses of 1.0–5.0 cg., and in larger doses (0.1 gm. maximal single dose) as a drastic cathartic, which, when given in too large doses, causes violent gastro-enteritis. Podophyllotoxin and colocynthin, even when given subcutaneously, cause diarrhœa and at times gastro-enteritis, and at the same time they cause inflammation of the kidneys and abscess at the site of injection. They are therefore unsuitable for subcutaneous administration.

Euonymin, a cathartic resin contained in Euonymus atropurpureus, is obtained as a precipitate on the addition of water to an alcoholic extract of the crude drug. After precipitation of euonymin from this solution, it still contains a glucoside which acts not as a cathartic, but which exerts a digitalis action on the heart (*Romm*).

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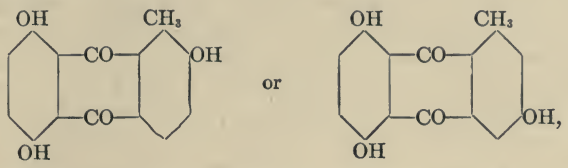
III. CATHARTICS ACTING CHIEFLY ON THE LARGE INTESTINE

This group is composed of a number of drugs which all contain anthraquinone derivatives, and particularly emodin, a trioxymethyl anthraquinone,



and, in still larger amounts, substances which are mostly glucosidal in nature, and from which, by hydrolysis or oxidation, different oxymethyl anthraquinones are formed in the intestine (*Tschirch*[1]). These active EMODINS are formed by hydrolytic cleavage of the glucosides of senna, rhubarb, and the different species of Frangula, and by cleavage and oxidation of certain constituents of aloes.

The oxyanthraquinones possess the power of electively exciting peristaltic movements of the large intestine, while they do not appear to produce any effect on the small gut. *Magnus* has shown that they exert their action locally in the wall of the large intestine. Consequently, small doses cause only the evacuation of soft not completely concentrated masses of fæces, while large doses, which cause a stormy peristalsis of the colon, produce profuse watery diarrhœa. *In any case they produce their effect after 8 hours or more,—i.e., they do not act until the drug has passed from the stomach into the colon. They are apt to produce more or less violent colicky pains and tenesmus.*

Among those organs which may be rendered hyperæmic as a result of irritation of the large intestine by drugs, particularly when the irritation and congestion are very pronounced, especial mention should be made of the female genital organs, which are innervated from the same nerve plexus, and which consequently may be reflexly influenced through the lower segments of the intestine. This action may, according to the circumstances, result in a desirable or undesirable increase in the menstrual flow of blood, and may also cause abortion in pregnant patients. A number of drastic purgatives of this last-mentioned group, particularly aloes, are consequently used and abused for this purpose.

EMODIN *is in part absorbed and passes into the urine, which may then take on a red color on the addition of an alkali. A certain portion is also excreted in the milk, imparting to it a cathartic action.*

SENNA leaves, obtained from Cassia angustifolia, contain, besides this active glucoside, a resin with a very bitter taste, which may be removed by extraction with alcohol without impairing the cathartic power of the drug. From 0.5 to 2.0 gm. in the form of an infusion suffice for a mild cathartic effect, while 2.0–5.0 gm. act after 5–8 hours

as a powerful purge. Senna leaves are the active ingredient of several official cathartic preparations,—for example, the compound licorice powder and the fluidextract of senna.

Among the FRANGULA species, Rhamnus frangula contains the largest amount of oxymethyl anthraquinone, about 5 per cent. When fresh, it contains emetic substances which disappear on keeping, and consequently this drug should be at least one year old.

The widely used extract of **cascara sagrada** is prepared from Rhamnus purshiana. From the fruit of Rhamnus cathartica a laxative syrup is prepared.

RHUBARB, or Rheum, the root of Rheum officinale, contains, besides the cathartic oxyanthraquinone compounds, a bitter and a large amount of tannic acid, the constipating action of which is alone evident when small doses—0.1–0.3 gm.—are given, but after larger doses—1.0–5.0 gm.—the laxative action preponderates.

ALOE, OR ALOES, the inspissated juice of the leaves of Aloe perryi, or socotrine aloes, and of Aloe vera, or Barbados aloes, both of which are official in the U. S. P., contains about 10–16 per cent. of aloin (*Grönewold*), a golden-yellow substance crystallizing in needle form, and considerable amounts of other anthraquinone derivatives (*Tschirch* [2]).

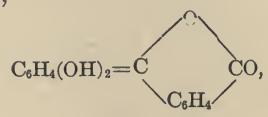
The administration of from 0.1–0.3 gm. of pure aloin is followed after 8–10 hours by catharsis, this effect occurring whether the drug be administered internally or subcutaneously. In the latter case in man it is almost completely excreted into the large intestine, where, just as after internal administration, it is probably transformed by oxidation into a cathartic substance. As this oxidation is accelerated by the presence of metal salts, particularly by that of iron salts, the powerful cathartic effects of the pilulæ aloes et ferri are explained. According to *Ellenberger* and *Baum,* aloes powerfully stimulates the secretion of bile.

The subcutaneous injection, best given in a 5–10 per cent. solution in formamide, causes considerable pain lasting for several minutes, but otherwise appears to be harmless (*H. Meyer, Balster*).

In the rabbit aloes does not act as a cathartic, and when subcutaneously injected it causes serious damage to the kidney (*Brandenberg*).

In addition to these drugs of vegetable origin, there are certain synthetically manufactured anthracene derivatives which have proved themselves to be useful cathartics. The knowledge that phenolphthalein acts as a cathartic is due to an accidental observation made by *v. Vamossy.*

PHENOLPHTHALEIN,



is a yellowish-white crystalline powder, hardly soluble in water, but soluble in olive oil in the proportion of about 2 per cent. With alkalies it forms red, readily soluble salts, which, when injected subcutaneously, cause violent irritation of the tissues, but which, when administered intravenously, are very slightly poisonous. Phenolphthalein itself, when injected subcutaneously dissolved in oil, readily causes evacuation of the bowels without causing local irritation.

Phenoltetrachlorphthalein, when injected subcutaneously (0.4 gm. in 20.0 gm. of oil), acts much more certainly, and the action persists for a number of days (*Abel* and *Rowntree*).

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[1] Tschirch: Arch. d. Pharm., vol. 237, 1899; vol. 238, 1900; Pharm. Post, 1904, Nos. 17–19, here lit.
[2] Tschirch: Schweiz. Woch. f. Chem. u. Pharm., 1904, vol. 42, No. 35.
v. Vamossy: Ther. d. Gegenw., 1902, p. 201.

Sulphur.—One of those substances which normally stimulate the peristalsis of the large intestine is sulphuretted hydrogen (*v. Bokay*), which is formed in small amounts in the large intestine from the cell detritus and other substances containing sulphur. The amount of sulphuretted hydrogen formed here can be markedly increased by the administration of sulphur, for sulphur, in finely divided form, is reduced not only by bacteria but also by the direct action of certain proteids, particularly by the proteids present in the mucous membrane of the large and small intestine (*Heffter*), and this reduction occurs both in the acid-reacting contents of the small intestine and in the alkaline ones of the large gut. On the other hand, the gastric mucous membrane does not contain substances which reduce sulphur. Consequently, when sulphur is administered, it is not changed in the stomach and produces no action there, but, starting in the small intestine and all the way down through the large intestine, it is transformed little by little into sulphuretted hydrogen, which stimulates the peristalsis.

As the sulphides of the alkalies have a caustic and destructive action on the tissues, this cathartic effect was formerly attributed to an irritation caused by them, but these salts are not formed in the intestine, as the high carbon dioxide tension of the intestinal contents completely prevents their formation. Consequently, even large doses of sulphur cause no appreciable caustic action or even inflammatory irritation of the intestinal mucous membrane, and hence no diarrhœa but only soft stools result from its administration.

Regensburger observed intestinal hemorrhages in dogs to which large doses (7.0 gm.) of precipitated sulphur had been administered, but it has not yet been determined whether these were the result of the caustic action of alkaline sulphides or were due to mechanical irritation produced by the fine particles of sulphur. It is also stated that sulphur has occasionally occasioned a fatal gastroenteritis in horses, but *Hartwig*, even after administering to a horse during 16 days as much as 3.0 kg. of sulphur, was able to produce only a chronic sulphuretted hydrogen poisoning, without any appreciable inflammation of the intestine (*Fröhner*).

Sulphuretted Hydrogen.—A portion of the H_2S which is formed is absorbed, and a part of this is oxidized further, so that the oxidized sulphur of the urine is markedly increased (*Krause*) when sulphur is ingested. Another portion remains unchanged, and is excreted through the lungs and the skin. It is possible that, with the continued use of sulphur, certain mild symptoms of general H_2S poisoning—such as headache, somnolence, muscular pains, and the like—may occur. However, certain authors (*Wood*) have attributed to the exhaled H_2S a curative action on the bronchial mucous membranes, where it perhaps causes a hyperæmia of the smallest blood-vessels and a stimulation of the bronchial secretion. Those springs containing sulphuretted hydrogen and alkaline sulphides have the reputation of being good expectorants and of producing curative effects in pulmonary catarrh. In veterinary practice the alkaline sulphides are employed in bronchial diseases.

In Metallic Poisoning.—Sulphuretted hydrogen has also the reputation of being useful in chronic metallic poisonings, such as those produced by mercury, lead, etc., and it is possible that it decomposes the compounds of these metals, which are fixed in the tissues or which are excreted into the intestine and perhaps reabsorbed, and that it aids in bringing about the final elimination of these metals in the form of their insoluble sulphides.

Sulphur is non-volatile, insoluble in water, soluble in ether, fats, etc. Sublimed sulphur (flowers of sulphur) is crystalline, while precipitated sulphur (milk of sulphur) is amorphous and forms a very much finer and consequently more active powder.

As Local Application.—Mixed with alkalies in pastes and salves it forms alkaline sulphides, and when these mixtures are applied to the skin these sulphides dissolve the horny structures, and consequently it is employed in the treatment of various skin diseases, such as psoriasis, pigmentation, etc.

Calcium sulphide, obtained by introducing H_2S into lime water, dissolves the hairs, and consequently may be used as a *depilating* agent.

CARMINATIVES

Carminative is the name given to a number of substances, to which are attributed the power of relieving distention,—*i.e.,* the power of driving along gases which have collected in the alimentary canal and which are causing discomfort. Among such are *chamomile*

flowers and *fennel* seeds, which are so often given to little children, and the *ethereal oils* obtained from these and many other drugs. Probably these substances have some power of exciting intestinal peristalsis, but perhaps it is only the mild local anæsthetic action of the ethereal oils which causes subjective relief of the discomfort.

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OBSTIPANTS, DRUGS WHICH RELIEVE DIARRHŒA OR CAUSE CONSTIPATION

From the foregoing it is evident that drugs may produce constipation either by inhibiting peristalsis of the stomach and of the intestinal secretions. The direct inhibition of both these processes by opium or morphine, and under some conditions by atropine, has already been discussed. Indirectly they may be inhibited by preventing stimulation or irritation of the intestinal mucous membrane either mechanically or chemically,—*i.e.*, primarily by withholding food, and secondarily by the administration of slimy substances of mucilaginous nature, such as gum arabic, decoctions of arrow-root, marshmallow-root, etc., which markedly interfere with chemical, and to some extent also with mechanical, irritation of the gastric and intestinal mucous membranes. Such an effect is also produced by the secretion of a large amount of a viscid mucus, containing large quantities of mucine, this being the natural protective reaction of the mucous membrane when chemically irritated.

If a reflex frog be suspended so that the hind legs hang in an acid solution of just sufficient concentration, the legs are drawn up after a few seconds, but if this solution contains colloid substances, such as gum arabic, gelatin, or the like, this reflex movement does not occur at all, or only very much later. In a similar fashion it is possible to demonstrate, on exposed nerves, raw surfaces, or other irritable tissues, the protective action of slimy substances against chemical irritants,—*i.e.*, against the rapid penetration into the tissues of chemical substances (*Tappeiner*).

Colloids, such as thin paste of starch or solution of vegetable slime, markedly retard the absorption of water and of substances, such as morphine or chloral, in watery solution; but they do not cause—and in fact they often check—diarrhœa, because peristalsis is slowed and consequently the fluid masses do not reach the large intestine.

Finely divided insoluble substances, such as suspensions of *talcum*,*

* *Debove* (*Progrès méd.*, 1883, No. 24) recommends for this purpose 200–600 gm. of talcum in milk.

creoline (*Stumpf, Görner, Levy*), or insoluble salts, act in a similar fashion, covering the surface of the mucous membrane with a thin coating and protecting it to a certain degree against the action of chemical agents.

Charcoal.—Mention should here be made of the protective action of finely powdered charcoal (either animal or wood charcoal) and its power of interfering with absorption. This substance possesses in a very high degree the power of absorbing substances dissolved or suspended in finely divided form in water, a property which is widely used in chemistry and in technical manufactures as a means of decolorizing fluids. According to *Wiechowski*, many poisons, such as phenol, strychnine, morphine, bacterial toxins, etc., are so completely absorbed and persistently retained by charcoal, when it is taken in sufficient amounts, that these mixtures of poison and charcoal are absolutely non-toxic, either in the alimentary canal or when injected subcutaneously. In accordance with this, it may be expected that if charcoal (10.0–30.0 gm. and more) be administered, it will combine with poisons or irritating substances, or even with bacteria which may be present in the alimentary canal, and will thus render them harmless, particularly if, by the subsequent administration of a cathartic, the charcoal with its absorbed poison be rapidly removed from the intestine.

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ASTRINGENTS

Finally, the astringents act in a similar but more complicated fashion. These are substances which form with the proteid constituents of the cells and of the secretions more or less stable colloid compounds, which are insoluble in neutral or weakly acid media. The chief ones are the various tannic acids, certain metallic salts, and calcium hydroxide.

The more viscid and less soluble these colloid compounds are the more decidedly will they harden the surfaces on and in which they are formed, and consequently the more effectively will they prevent their own further penetration and that of other substances into the deeper-lying protoplasms and cells.

They act in a similar fashion to the membrane formed in the wall of a diffusion cell by precipitation of ferrocyanide of copper, which renders these cells impermeable to substances in solution. Consequently, with the true astringents coagulation and the resulting death and destruction to the protoplasm are limited exclusively to the most

superficial layers of the tissues, which are, as it were, tanned, and which form a protective coating against chemical, bacterial, and even against mechanical action, and thus protect against all sensory and inflammatory irritation. At the same time the secretory activity of the superficial glands which come in contact with the drug are diminished (*Schütz*), and the exudation of fluid from wounds or granulation tissues is stopped.

Finally, astringents also bring about changes in the superficial capillaries and arterioles, whose walls become less permeable to the plasma and leucocytes, because the cement substance between the endothelial cells is rendered less permeable, while at the same time the circular muscular fibres contract and the vessels are narrowed as a result of the coagulation of their proteids (*Heinz*). The tissues consequently become, at least in their most superficial layers, more anæmic, firm, and dry, and less sensitive. These are all effects which counteract swelling, redness, active secretion, and irritability of inflamed tissues. Consequently, astringents are employed in inflamed wounds of mucous membranes as a means of relieving these conditions, and particularly in the treatment of catarrhal inflammation of the gastric and intestinal mucous membranes.

Caustic Actions.—When astringents are at the start applied in concentrated solution to a mucous membrane or to granulation tissues, they not only coagulate the most superficial layer, but, before the protective layer has had time to form, they penetrate deeper and cause the destruction of the deeper tissues. In such case they may produce considerable caustic effects, the degree and depth of which, it is clear, will depend on the diffusibility and solubility of the drug, and also on the chemical character of the drug itself as well as on that of the combination formed between it and the constituents of the tissues. If the eschar formed is not firm and tenacious but is soft or even fluid, it opposes no resistance to the further penetration and deeper action of the drug. Consequently, if a caustic substance possesses a strong chemical avidity for the body tissues (with the caustic metal salts it is chiefly the acid components which exhibit such avidity), it may, even in the low concentrations, produce considerable destruction of the tissues. Such more extensive destruction and death of the tissues will in this case, as always, cause an inflammatory reaction, with dilatation of the capillaries, etc., which will finally end with the casting off of the necrotic masses and the regeneration of new tissues.

The tannins are a number of non-nitrogenous amorphous colloid substances, present in almost all plants, readily soluble in water, glycerin, and alcohol, and entirely insoluble in water-free ether, which all possess the properties of precipitating albumin, gelatin, and vegetable bases in neutral or weakly acid solutions, and of coloring iron salts dark blue or green. They are weak acids, chiefly anhydrides

and condensation products of different dioxy- or trioxybenzoic acids, particularly of gallic acid, which is formed when they undergo hydrolytic cleavage under the influence of alkalies or ferments. *While gallic acid gives the above-mentioned ink reaction with iron salts, it precipitates neither albumin nor gelatin, and consequently is without astringent action.*

TANNIN, or TANNIC ACID, is a yellowish powder obtained from nut-galls. It possesses an astringent taste and acts as an astringent in the above-described fashion, and, under certain conditions, may produce a superficial caustic effect. It may be used as an astringent application to all accessible mucous membranes or granulating surfaces,—for example, as a gargle or local application, in ½–1 per cent. solution, in inflammation of the throat.

Action in Alimentary Canal.—It is not well adapted for oral administration in the treatment of intestinal catarrh, because it produces its astringent effects chiefly on those tissues with which it first comes in contact,—namely, the gastric and duodenal mucous membranes,—and thus disturbs the appetite and digestion, and because in the small intestine it undergoes hydrolytic cleavage and absorption, and consequently does not pass far enough down in the gut.

Reputed Action after Absorption.—Gallic acid after absorption is almost completely combusted, but a small portion is excreted in the urine, either unaltered or in conjugation with sulphuric acid (*Mörner*). Tannic acid itself or as an alkaline tannate does not pass into the urine; this is quite evident from the fact that any human urine which contains no albumin, whether acid or alkaline, forms an insoluble precipitate with tannic acid, even in the proportions of 1: 100,000. This same precipitate is also formed on the addition of tannin to the clear urine which is passed after ingestion of tannin (*Rost*[1]). From these facts it is probable that, during or before its absorption by the intestinal mucosa, tannic acid is completely transformed into gallates of the alkalies, which possess no astringent properties. Consequently, an astringent or styptic effect in the lungs, kidneys, etc., cannot result from the oral or any other administration of tannin.

Drugs Containing Tannin.—When it is desirable that tannic acid reach the lower portions of the intestine, drugs are used which contain tannin inclosed in cellulose or in mucilaginous or other substances which protect it from too rapid solution and absorption. Such drugs as *rhatany, krameria, quercus alba, kino,* etc., in the form of their extracts or decoctions, fulfil this indication.

The large amounts of tannin present in many drugs which are used for quite different indications often produce undesirable effects, as is the case with extracts of calisaya or pomegranate-root bark. Radix ipecacuanhæ, which we have already studied in the section on emetics, also contains large amounts of tannic acid, and it is probable that it is for this reason that it is used in the treatment of dysentery [?—see p. 182.—TR.]

TANNIC ACID COMPOUNDS.—The desirable effects, however, are much more certainly and completely obtained by the administration of synthetically manufactured tannic acid compounds in which the tannic acid is firmly combined. These are almost tasteless powders,

which produce no astringent effects in the mouth or in the stomach, but which are gradually dissolved in the alkaline intestinal juices, with the liberation of tannin in an active form.

Tannalbin is such a compound, and is a tannin albuminate containing about 50 per cent. of tannic acid, which is rendered resistant to gastric digestion by heating to 110–120° C. (*Gottlieb*). This is gradually broken up by the pancreatic juice, and consequently exerts its action throughout the alimentary canal as far down as the colon and rectum. Its dosage is 1.0–2.0 gm. several times daily.

Tannigen.—Another is tannigen, or diacetyl tannin, a yellowish-gray powder insoluble in neutral and acid fluids, with a mild acid taste, which contains about 85 per cent. of tannin. It is dissolved by weak alkalies, such as the carbonates, borates, etc., and, in such solutions, precipitates albuminates and gelatin. When given in rather large doses (0.5–4.0 gm.), it passes through the bowel down into the large intestine, where it may be found in part as unchanged tannigen but in part in the form of tannic acid (*H. Meyer u. F. Müller, Rost* [2]).

Tannocol, a compound of tannic acid with gelatin, containing about 45 per cent. of tannin, and *tannoform,* a condensation product of tannin and formaldehyde, are substances with the same general properties.

Coto.—In this connection mention may be made of coto-bark decoctions, which are employed, particularly in Italy, as curative agents in diarrhœa. The active constituents of this bark is not a tannin, but a very irritant bitter, cotoin, which is employed in doses ranging from 5.0–50.0 mg. Very little is known concerning its action on the intestinal mucous membrane.

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METALLIC SALTS

Of the astringent metallic salts only those are suitable for the treatment of inflammation of the gastric and intestinal mucous membranes which neither cause vomiting nor readily produce caustic effects on the mucous membranes. These requirements are best met by the insoluble

Bismuth subnitrate, the dose of which is 0.2–1.0 gm. or more several times a day. It forms on the mucous membrane a firmly adhering coating (? Tr.), toughening and protecting it and diminishing its secretory activity. Unless the mucous membrane is eroded, bismuth subnitrate is not absorbed, and consequently as large amounts as one desires may be given without danger of poisoning by absorption of the metal. This salt is to-day often used by röntgenologists

for the purpose of observing or photographing the stomach and intestine and their movements.

Danger of Nitrite Poisoning.—However, such employment carries with it some danger from another source, for abnormally active bacterial fermentation in the large intestine reduces the nitrate to a nitrite, which may be absorbed in considerable amounts. As nitrites are poisons to the blood, very small amounts of which may cause death, this danger should be avoided, and, consequently, in röntgenologic work the basic bismuth sulphate or chloride or oxide should be substituted for the subnitrate.

Cattle and deer may suffer from the same toxic action on the blood if they consume considerable amounts of saltpetre spread upon the fields as a fertilizing agent. If sodium nitrate is not rapidly absorbed, but remains for a considerable time in the stomach, it may be reduced and transformed into a lethal poison (*Böhme, E. Meyer, Hoffmann u. Bennecke*).

In the large intestine bismuth subnitrate and other bismuth salts combine with H_2S and form the deep-black bismuth sulphide, and in this fashion one of the effective stimuli of peristalsis is removed and consequently peristalsis becomes less active (*v. Bokay*).

Other basic insoluble bismuth compounds used in medicine in the same fashion as the subnitrate are the *subgallate* and *subsalicylate*, the former of which carries the commercial name of dermatol.

Lead acetate, or sugar of lead, is soluble in water, and consequently should be employed only in weak non-corroding concentrations. The dose is 0.1 gm. (!) per dose, 0.3 gm. (!) per diem. It is a powerful astringent, constricting the vessels quite markedly, and is slowly absorbed, and, therefore, when used for a long time may cause poisoning. This salt could be entirely dispensed with for internal use, and the same is true of

Alum, which, although a good astringent and one which when absorbed does not cause any poisoning, readily causes gastric irritation or vomiting, even when administered in small amounts.

Silver nitrate has also been much used as an astringent in the stomach and intestine. As a large part of it is changed in the stomach into silver chloride, which is insoluble in water containing hydrochloric acid, but which is somewhat soluble in the presence of chlorides of the alkalies, it is probably entirely ineffective in the stomach. [With this sweeping statement clinicians will hardy agree.—Tr.] When administered by mouth, however, there can be little doubt that silver nitrate never reaches the lower portion of the intestine in an active form, for it is rapidly reduced to metallic silver by organic substances present in the stomach and intestine.

A small portion is absorbed probably as an albuminate and distributed throughout the body by the lymph, where it is deposited in the various tissues in the form of a reduced metal (*Fraschetti*). In this fashion the various organs—and, in man, especially the skin—

are colored slate-gray, from which in other particulars no harm results. This condition is known as argyria.

Calcium hydroxide, chiefly used as lime water, which contains 0.15 per cent. of $Ca(OH)_2$, forms insoluble soaps with the fatty acids, and thus toughens the lipoid constituents and the intercellular cement substances of the tissues, an action which may be aided by the mechanical protective action of the calcium carbonate which is formed on the surface of the mucous membranes. The very slight concentration of lime water renders it impossible for it to cause any corrosive effect, while its alkaline nature enables it to dissolve the tenacious mucus adhering to the inflamed mucous membranes and thus to produce a cleansing effect (*Harnack*). As an alkali, it can also neutralize harmful acids, such as are formed in the acid intestinal catarrh of nursing infants (*Baudnitz*). The constipating effects of lime water or of waters containing calcium are probably also due in part to the action exerted by the lime salts, after their absorption on the vegetative nervous system, the excitability of which they depress, and in part to their effects on the capillary vessels, the permeability of which they lessen (*Chiari u. Fröhlich, Chiari u. Januschke*) (see p. 495).

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CHAPTER VII

PHARMACOLOGY OF THE REPRODUCTIVE ORGANS

NERVOUS AND CHEMICAL CORRELATION

LIKE those of the alimentary canal, the functions of the genital organs, with their glands and unstriated muscles, are controlled partly by manifold nervous reflexes and partly by the direct action of various stimulating substances which reach them in the blood stream. While formerly the relationship between the different functions of the genital organs with each other and with numerous other functions were attributed exclusively to central nervous influences, it has more recently been proved that the genital organs influence the development and function of distant tissues and organs chiefly by means of their internal secretions,—*i.e.*, by chemical agents (hormones).

The Ovaries.—Thus, the importance of the ovaries for the development of the other female sexual organs is well known. In animal experiments, after extirpation of the ovaries in young subjects the uterus and tubes remain rudimentary (*Hegar, Kehrer*), but, if the ovaries are transplanted under the skin, normal development of the uterus and tubes occurs (*Halban*). The connection between the periodic changes, which the uterine mucous membrane undergoes, and the associated changes in numerous bodily functions, are also, at least in part, due to the action of chemical substances which are formed as the ovum matures, for *Knauer* observed the occurrence of "heat" in animals in which the ovaries had been transplanted to other parts of the peritoneal cavity.

BOTH THE TESTICLES AND THE OVARIES form chemical substances, which exert an influence on other portions of the genital system and on many other parts of the body. This highly specialized tissue is very readily destroyed by the action of *X-rays*, so that the application of these rays leads to atrophy of testicles or ovaries, and thus to all the indirect results of a cessation of the function of these organs. In practice the ovaries are at times thus treated. The ovarian follicles appear to be very susceptible also to certain toxic substances at times present in the blood, so that, for example, sterility and retrogression of the pregnancy may be produced by injections of choline (*v. Hippel* and *Pagenstecher*).

It is this more or less sudden cessation of the ovarian influences which causes the manifold disturbances following ovariotomy and the menopause. Reliable observations indicate that they may be favorably influenced by the internal administration of ovarian tissue (*Chrobak, Landau*).

Other functions connected with the function of reproduction, as well as those of the reproductive organs, are also influenced by the internal secretion of the germ-glands. Examples of this are as follows: The callosities on the thumb and certain muscles of the forearm

of the brown frog hypertrophy at the rutting season. This does not occur in castrated frogs if a piece of testicle is put into the dorsal lymph-sac and gradually absorbed (*Nussbaum*). The complete development of all the secondary sexual characteristics is also influenced by the germ-cells, as are the growth of bone and the general metabolism. As far as the effects of these internal secretions on other functions are definitely known, they will be discussed elsewhere, but we are far from possessing anything like a complete knowledge of the internal secretions or of their actions. *For this reason, their therapeutic employment with clear indications is at the present time extremely limited.*

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Erection.—Among the secondary sexual characteristics which first become evident at puberty, and which depend on the internal secretions of the testicles, is the development of a specific sensibility of certain lower nervous centres, which are involved in the function of reproduction. The complicated reflexes which induce erection are primarily dependent on psychic processes, and may be excited or inhibited from the cerebral cortex, or may, on the other hand, result from peripheral stimuli.

Yohimbin, an alkaloid contained in the yohimbe bark (W. Africa), apparently is able to increase the excitability of the centres for erection in the lumbar cord, even in doses which do not affect the excitability of other centres there, such as that for the patella reflex (*Fr. Müller*). At the same time it causes a local dilatation (by direct action on the vessel walls) in various vascular systems, but most especially so in the vessels of the penis, and there results a marked increase in the amount of blood flowing out of the dorsal vein of the penis. It is probable that other reputed aphrodisiacs favor erection by local vasodilating actions. The aphrodisiac effects of *cantharidin* and certain other drugs, which are excreted by the kidney and set up an inflammatory irritation of the urogenital tract, are probably due to such sensory irritation and its accompanying vasodilatation.

MAMMARY GLANDS

A most interesting nervous and chemical correlation exists between the genital system and the function of the mammary glands, the growth of which in the female at puberty is doubtless due to a stimulus coming from the ovaries.

Observations on animals have shown that the development of these glands is retarded after double oöphorectomy, but proceeds quite normally after successful transplantation (*Foges, Kramer*). The changes in the breast during pregnancy also occur independently of any nervous influences, for after successful transplantation of these glands their growth and active secretion have been observed in pregnant guinea-pigs (*Ribbert*). The hormone here appears to be a product of the fetal metabolism, for injections of fetal extracts excite hypertrophy of the mammary gland in virgin animals (*Starling* and *Claypon, Foa, Biedl*).

Lactagogues.—The inauguration of the lacteal secretion after delivery is likewise in part due to chemical stimuli, and apparently also in part to the cessation of an inhibitory influence which is exerted by the fetal substances which stimulate the growth of these glands (*D'Errico*). Very recently several investigators (*Basch, Lederer* and *Pribram*) have demonstrated the presence of galactagogue substances in *placental extracts,* injection of which increases the milk secretion of goats.

This secretion, moreover, may be influenced by numerous nervous influences, and especially by manifold reflexes, among which those from the genital organs and that from suckling are especially important. The innervation of the lacteal glands must, however, be entirely different from that of the other true glands, *for even such a typical stimulant of glandular activity as pilocarpine produces no effect on the milk secretion* (*Hammerbacher*). While, generally speaking, this secretion depends on the general state of nutrition, *it can in no way be influenced by feeding special food-stuffs, nor has it been proved that it can be influenced by pharmacological agents. Of true medicinal galactagogues there are none,* but, on the other hand, it is claimed that the secretion of milk may be distinctly lessened by the administration of KI.

Elimination of Drugs in the Milk.—That many foreign substances may pass into the milk has been definitely established, the following having been demonstrated in human milk after their medicinal administration: iodine, bromine, salicylic acid, antipyrine, arsenic, and mercury (*Bucura*), while alcohol, morphine, and atropine have been found in the milk of animals. However, only very small amounts of such foreign substances are present in the milk.

The excretion of antitoxins through the lacteal glands (*Ehrlich*) appears to be of great significance in connection with the transference of protective substances to the suckling.

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THE PHARMACOLOGY OF THE UTERINE MOVEMENTS

Although the same pharmacological principles hold good for the treatment of disease of the mucous membranes of the genital tract as

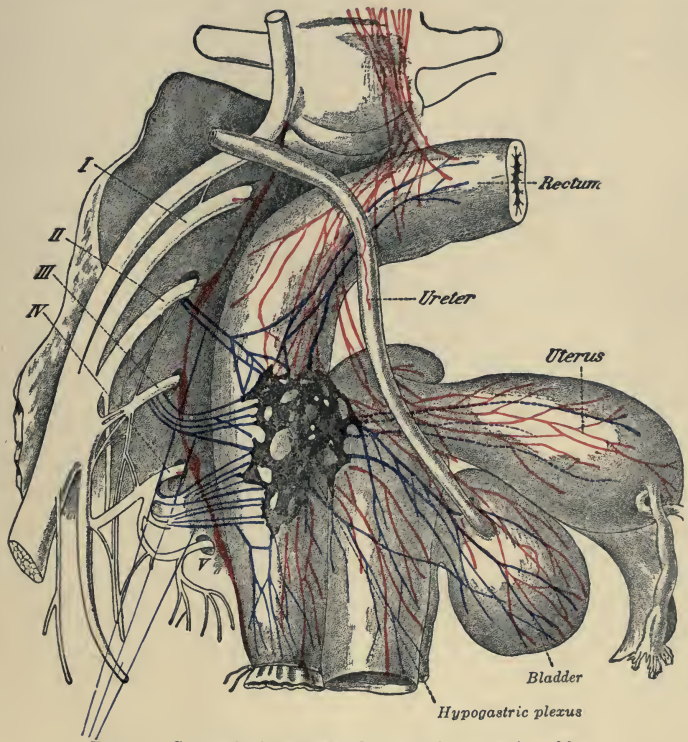

Fig. 16.—Sympathetic nerves, red; nervus hypogastricus, blue.

for the other mucous membranes (see Pharmacology of Inflammation, p. 481, and Disinfection of the Mucous Membranes, p. 508), the pharmacology of the uterine movements deserves special attention.

Like the intestine, the uterus *in situ* or when isolated manifests pendulum movements and peristaltic contractions, and these phenomena may be studied for hours in the perfused uterus (*Kurdinowski*[1]) or in one surviving in Ringer's solution which is kept saturated

with oxygen (*Kehrer*[1,2]). It is thus evident that this organ contains within itself the factors necessary for its automatic contractions, which vary according to the state of the uterus, occurring most frequently in the early stages of pregnancy, and later becoming less frequent but more powerful, being separated by long periods of inactivity.

Innervation.—The uterine movements, like those of other organs containing smooth muscle, are regulated by the central nervous system, receiving from it motor and inhibitory impulses through the sympathetic and probably also through the sacral autonomic nerves (see Fig. 16). The Nervus pelvicus (erigens), whose fibres arise from the second, third, and fourth sacral roots, supplies the rectum, anus, bladder, and the external genitals, and probably also the uterus, with sacral autonomic fibres, while the hypogastric nerve, which arises from the inferior mesenteric ganglion, and the spermatic nerve, from the spermatic ganglion, belong to the true sympathetic system proper. The uterine ganglion lies more peripherally in the neighborhood of the cervix. Much uncertainty still prevails as to the influence exerted on the uterus by these different nerves, for not only is the anatomical arrangement complicated, but, in addition, their different behavior in different species renders it most difficult to determine definitely their physiological significance.

Effects of Epinephrin and of Stimulation of the Sympathetic.—According to *Langley* and *Anderson,* in the cat stimulation of the hypogastric at first produces chiefly stimulation of the inhibitory fibres, while in the rabbit it causes excitation from the start. Epinephrin acts on the uterus quite analogously to the stimulation of these sympathetic fibres, causing in the cat first inhibition and then excitation, but in the rabbit immediate excitation.

Effects of "Autonomic" Drugs and of Stimulation of Autonomic Nerves.—The influence of the nervus pelvicus is still more uncertain, for this nerve carries vasodilating nerves to the uterus (*v. Basch* and *Hofmann*), and stimulation of its trunk excites uterine contractions (*Röhrig, F. Kehrer*), which last effect, according to *Langley* and *Anderson,* is due only to its containing some fibres from the hypogastricus, which join it deep down in the pelvis. Pharmacological observations, however, indicate that the pelvic nerve also contains motor nerves, which actually come from the sacral autonomic system, for that group of drugs which in general act on the autonomic nerve-endings produce a decided effect on the uterus. Thus, *pilocarpine* and *physostigmine* excite violent uterine contractions, which may become tonic in character, while here, as in the intestine, *atropine* in small doses causes excitation and in large doses cessation of the movements of the uterus (*E. Kehrer*[1,2]).

DIFFERENT REACTION OF THE GRAVID AND NON-GRAVID UTERUS

Nicotine produces different effects in different species of animals, and also in the gravid and non-gravid uterus, primarily inhibiting and later exciting the empty organ and immediately exciting the gravid one. *Epinephrin,* too, exhibits a similar difference in the effects produced by it in the gravid and non-gravid uterus

(*Dale, E. Kehrer*[1,2]). The difference in the reactions of the gravid and non-gravid uterus to these drugs is in accord with the influence of sympathetic stimulation in the two conditions for it has been found that in the cat stimulation of the hypogastric nerve inhibits the non-pregnant uterus but excites the pregnant one (*Langley* and *Anderson, Dale*). It would, therefore, appear that the stretched muscle-fibres of the gravid uterus are more susceptible to all exciting agents than those of the empty organ (*Cushny*). This is in accord with clinical experience.

Hypophysis Extracts.—Recently it has been found that the extract made from the infundibular portion of the hypophysis, *pituitrin,* excites maximal contraction of the rabbit's uterine muscle and renders it more susceptible to motor stimuli (*Frankl-Hochwart* and *Fröhlich*).

Pilocarpine and Nicotine.—The above-discussed action of pilocarpine is the ground for its employment as an oxytoxic (*Brennecke, Kleinwächter*), while the excitation of the uterine contractions produced by nicotine is of toxicological interest on account of the occasional unjustifiable employment of an *infusion of tobacco as an abortifacient.* Besides those already mentioned, *numerous other drugs* act on the terminal nervous mechanism in the uterus. Among these is *quinine,* which is much used to strengthen lagging pains (*Bäcker, Mäurer, Conitzer*), excites contractions in the surviving uterus and hence must act peripherally (*Kurdinowski,*[2] *E. Kehrer*[3]). Small doses of *morphine* excite (while large ones inhibit) uterine contractions (*E. Kehrer*[4]). Bearing in mind the difference in individual susceptibility to *morphine,* this difference in the effects of small and large doses accounts for the contradictory clinical views concerning the effect of morphine on parturition. In this connection it is of interest that *scopolamine* appears not to affect the uterine contractions appreciably.

DRUGS WHICH INFLUENCE THE UTERINE CONTRACTIONS CENTRALLY OR REFLEXLY

In addition to being affected by these peripherally acting agents, the uterine contractions may be influenced by many agents which act on the central nervous system (centres in the lumbar cord), as, for example, by anæmia or asphyxia, both of which strengthen the contractions. These spinal centres are, moreover, under the control of higher centres, some of which are situated in the cerebral cortex and may be influenced by reflexes of the most varied origin, especially from the nasal mucous membrane (*Fliess, Schiff*). Toxicologically it is important to remember that, simultaneously with peristalsis, uterine contractions may be reflexly excited by chemical irritation of the intestinal mucous membrane (*E. Kehrer*[4]). It is for this reason that *drastic purgatives*—for example, *aloes*—may excite uterine contrac-

tions and cause abortion, not only by causing hyperæmia of the pelvic organs but also by causing reflex stimulation of the uterine contractions. The same holds for other abortifacients, such as the ethereal oils of *Tanacetum vulgare* (*tansy*), *Thuja occidentalis* (*arbor vitæ*), *Taxus baccata* (*yew tree*), *Juniperus sabina,* etc., which all cause gastro-enteritis and at the same time may cause abortion. The extent to which specific effects on the uterus also contribute to this result has not yet been settled. Why uterine hemorrhages, abortions, and miscarriages occur after large doses of salicylic acid is entirely unknown (*Binz*).

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In practice, ergot, hydrastis, and cotarnine, and quite recently epinephrin and pituitrin, are employed for the purpose of exciting or strengthening uterine contractions.

ERGOT

Ergot (Secale cornutum) is the sclerotium of the fungus Claviceps purpurea, which causes a fungous disease in various grains, especially in rye during wet seasons.

In former times ergot caused very severe epidemics of ergotism, and even in recent decades such epidemics have occurred in many civilized countries. (1867–8 in East Prussia, 1894 in Nanterre, France, 1907–8 in Hungary, and in numerous years in various districts in Russia.) When ergot is ground with the grain, as much as 6–10 per cent. may be present in bread and foods made from the flour, and even ½–1 per cent. is enough to cause poisoning. In epidemics two types of disease occur, a convulsive and a gangrenous type, one type or the other being usually the prevailing one in a given epidemic, although epidemics have been described in which one type alone was observed (*Kobert* [1]).

The varying clinical picture of spasmodic or convulsive ergotism starts with a feeling of numbness in the fingers, which spreads over the whole body; later gastro-intestinal disturbances, with vomiting and purging, develop, and still later the typical spasms. These consist in very painful tonic contractions of the muscles, occurring at intervals and affecting especially the flexors of the extremities and leading to typical contractures. In addition, there may finally occur clonic epileptiform convulsions, which may last for hours. The contractures remain permanently, and with them serious disturbances of the nervous system, such as pseudo-tabes or imbecility.

Gangrenous ergotism also often starts in the same way, with prickling and numbness of the fingers, vomiting and diarrhœa, and after some days the typical lesions of gangrene. In these the skin over the affected parts loses its natural color and turns black and blue, the epidermis is raised up over the gangrenous spots, and dry gangrene of whole toes and fingers may result, and at times also of the ears or nose. The development and limitation of the gangrene is at first accompanied by very severe pain, but later complete anæsthesia develops.

During such epidemics abortions and miscarriages are often observed, and consequently as early as the 17th century ergot was employed as an oxytocic. On account of its abuse, the drug soon fell into disrepute, and its use was much opposed and was even forbidden at the end of the 18th century, but early in the 19th century it was re-introduced into therapeutics.

Practical experience obtained from the use of ergot indicates a threefold action of the drug,—the first that of exciting spasms, which is responsible for the convulsive ergotism; the second that of causing gangrene, which is responsible for the gangrenous ergotism; and the third and most important, its action on the uterus. In addition, active preparations of ergot cause vasoconstriction and a rise in blood-pressure. In spite of many laborious investigations, for a long time little advance was made in determining which constituents of ergot were responsible for these different actions, but recent efforts have been more successful.

Active Principles.—Extracts of ergot are mixtures of complicated and inconstant composition, from which there have been prepared at least three pure substances, which are concerned in its pharmacological actions. One of these, ergotoxin (*Kraft, Barger, Carr* and *Dale* [1,2,3]), an amorphous alkaloid, exerts the specific characteristic action of ergot. In addition to it, ergot extracts contain at least two physiologically very active ptomaine-like bases, which are formed either by the metabolism of the fungus or by the actions of micro-organisms on organic mother substances (*Barger* and *Dale* [1,3]).

Inactive Constituents.—Besides these three active ingredients, ergot contains a large number of less active substances,—for example, leucine (*Buchheim, Barger* and *Dale*), uracil, tetra- and pentamethylenediamine, betaine, and choline (*Riclander*). As a means of recognizing the presence of ergot in bread and flour, considerable interest attaches to *sclererythrin*, a red coloring matter of acid character, which, along with other coloring matters, occurs in the drug combined with Ca and Mg. It passes readily from acidified water into ether and may be readily identified chemically and spectroscopically.

Ergotoxin.—According to a number of investigators (*Kraft, Barger, Carr* and *Dale* [1,2,3]), there is present in ergot a crystalline alkaloid, ergotinin, first prepared by *Tanret*. This has no action on the uterus, but is accompanied by its amorphous hydrate, hydro-ergotinin or

ergotoxin, which apparently is *the most important constituent* of the drug. According to *Dale,* when administered subcutaneously or intravenously this substance causes contraction of unstriped muscle, especially of the uterine muscle, a rise in blood-pressure due to vasoconstriction, and also the characteristic ergot gangrene. The rise in blood-pressure is due to peripheral action and is very persisting, but after large doses this primary excitation of the vasoconstrictor nerve-endings is followed by an elective depression of the pressor sympathetic nerves, so that the blood-pressure falls and can no longer be raised by epinephrin, but under these conditions is actually lowered by it (*Dale's* vasomotor paradox).

Aqueous extracts of ergot also contain two very active bases, which in their actions closely resemble epinephrin, *parahydroxyphenylethylamine* (*Barger* and *Dale* [1,2]), formed from tyrosine in the mycelium of the fungus by bacterial action, which is a very powerful vasoconstrictor, and *β-imidazolylethylamine* (*Barger* and *Dale* [3]), similarly formed from histidine, which even in enormous dilutions excites violent uterine contractions.

Other Alkaloids.—Formerly the specific actions of ergot were attributed to various alkaloids (*Kobert*[2]) and resinous substances combined with them (*Jacobi*).

Among these alkaloids the substance known as cornutine for a time attracted considerable attention, but later investigations have shown it to be, not a pure substance, but a mixture of various alkaloids, among which is ergotoxin, and that it has little or no therapeutic activity. It is, however, possible that this mixture of alkaloids known as cornutine, and perhaps their decomposition products, which are present in ergot, are responsible for the convulsive actions of ergot, for it causes typical tonic and clonic convulsions and behaves like a typical convulsant. As, however, it is not always a constituent of ergot and as no one has yet succeeded in producing chronic poisoning in animals by its administration, its significance for convulsive ergotism is still uncertain (*Schmiedeberg*). Cornutine excites uterine contractions by an action on the central nervous system, but some observers have found it effective in surviving uterus, which may be explained by its containing ergotoxin.

Resinous substances which are present in ergot, combined with inert alkaloidal substances, have also been considered as the constituents responsible for the specific effects of the drug. Among such are sphacelic acid (*Kobert*[3]) and sphacelotoxin, which latter, although possessing no true acid properties, readily combines with other substances, forming, among other compounds, chrysotoxin and secalintoxin (*Jacobi*). According to more recent investigators (*Kraft, Barger* and *Dale*[4]), these are not chemical entities, *Dale* claiming that the nitrogenous component of the mixture is identical with ergotoxin. *Kobert*[3] and *Jacobi,* from their observations on animals, believed that the poisonous resinous acids and their salts were the substance which caused the gangrene, but recently *Kraft* and *Barger* and *Dale* have attributed this effect to ergotoxin.

Experimentally the gangrene is best produced in the cock's comb and in the pig's snout. It is due to a peculiar change occurring in the vessel walls, a hyaline thrombosis of the smallest arteries, which develops in the periphery as a result of the stasis resulting from the toxic contraction of the vessels.

From this short survey of the more important points bearing on the chemistry of ergot and its constituents, it is evident that much uncertainty still obtains as to the chemical properties and the homogeneity of the various substances prepared from it, and also as to their

activity. In view of these contradictions especially, little may be maintained with certainty as to the chemical composition of the constituents which cause the specific effects on the uterus.

There is no doubt, however, that this substance—or these substances—are readily extracted by water and less readily by alcohol. The fact that such difficulties have attended the efforts made to isolate the substance acting on the uterus, and that repeatedly new substances have been described as the true active principle, is due both to the marked instability of the active substances and to the very active reaction of the uterus, especially when gravid, to various toxic substances, central excitants acting on the uterus through the centres while the sympathetic and autonomic poisons act on the nerve-endings in the uterus itself. In addition, the interpretation of experimental results is rendered still more difficult by the fact that the uterus may be affected by various reflexes and by such factors as asphyxia, in such fashion that it may appear that it is directly affected by a drug when this is not the case.

Instability of the Active Principles.—As the substances acting on the uterus so readily undergo change, the apothecary should renew his supply each year. [This is legally obligatory in Germany.—Tr.] Ergot is most active before the rye has ripened. When stored its specific (uterine) activity gradually diminishes, until at the end of a year it possesses only one-seventh to one-eighth of its original activity, and at the end of two years only one-fifteenth (*E. Kehrer*). The substance causing gangrene appears to be even more unstable, for the effect on the cock's comb, according to *Kobert* and *Grünfeld,* can be obtained only in the first few months following the harvest, being markedly weaker in November and having entirely disappeared by the following March.

Physiological Assay.—This effect on the cock's comb (*Kehrer*), the action on the blood-pressure (*Dale, Wood* and *Hofer*), and the excitation of the surviving cat's uterus (*Kehrer*), have all been employed as methods of physiological assay. As these different effects are in part due to different constituents, it is evident that the results of the assay will vary with the method employed (*Cronyn* and *Henderson*). As ergot is chiefly employed for its effects on the uterus, *the most rational assay method is that in which the cat's uterus is employed.*

It can be demonstrated that ergot extracts excite contractions in the uterus surviving in Ringer's solution, increased tone and strengthening of the autonomic contractions resulting from ordinary doses, and tonic contractions from larger ones. This action is, therefore, a peripheral one, agreeing qualitatively with the effect of intravenous injection of active extracts on uterine movements in the living animal. *Ergotoxin and β-imidazolylethylamine are the only two substances*

which have thus far been prepared in pure form and which produce this characteristic action.

Vasoconstrictor Action.—Certain of the active principles of ergot also act on the vessel walls or on the vasomotor nerve-endings in them, and, therefore, active ergot extracts may raise the blood-pressure. This action is also a peripheral one, and appears to be due to ergotoxin and hydroxyphenylethylamine.

Therapeutic Employment.—In obstetrical practice ergot is no longer used to strengthen uterine contractions during labor, for the inconstant strength of its preparations renders the dosage uncertain, and, therefore, there is danger of causing tonic contraction of the uterus and death of the child; but, after delivery of the child and loosening of the placenta, it is generally used for the purpose of checking hemorrhage and to bring about a firm and lasting contraction of the uterus. The effects in checking hemorrhage under such conditions have been attributed to a contraction of the uterine vessels under the influence of the drug, but this is not strictly the case. However, the contraction of the uterine muscle, which is excited by ergot, itself acts to check bleeding, for the uterine vessels are enclosed in a mesh of uterine muscles, and when the muscles contract they are compressed so that the formation of thrombi is favored. This is the reason why ergot is so efficient in checking uterine hemorrhage, although its action on other hemorrhages is so uncertain. The stoppage of uterine hemorrhage could be attributed to a direct action on the vessels only on the hypothesis that only the uterine vessels are constricted and that no extensive vasoconstriction occurs elsewhere, for otherwise a general rise in blood-pressure would result and the checking of the hemorrhage would actually be rendered more difficult.

Preparations.—In addition to powdered ergot, numerous other officinal and non-officinal preparations are employed. [In this country the fluidextracts are almost exclusively employed. For practical purposes an aseptic, physiologically assayed fluidextract is to be preferred, but such preparations also become inert quickly, and therefore an effort should always be made to secure a fairly fresh preparation.—Tr.] It is to be hoped that before long these preparations of inconstant composition and uncertain strength will be superseded by the therapeutically valuable substances in pure and stable form. Until this is attained it is desirable that a satisfactory method of physiological assay should be devised and worked out thoroughly (*Gottlieb*).

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Preparations of hydrastis and of cotarnine are also employed in uterine hemorrhage. Hydrastine, from Hydrastis canadensis, and its derivative hydrastinine, also possess a peripheral exciting action on the uterus (*E. Kehrer*). Both alkaloids, but more especially hydrastinine, cause a general vasoconstriction and a rise of the blood-pressure, due both to a stimulation of the vasomotor centres and to a peripheral vasoconstricting action (*Falk, Marfori*). An entirely similar effect on the uterus is produced by *cotarnine*, which is a methyloxyhydrastinine prepared from narcotine, an inactive opium alkaloid (*Freund*). This drug, like the others, also acts on the uterus directly. Its hydrochloride and its phthalate are obtainable under the trade names of stypticin and styptol, and are employed in the treatment of uterine hemorrhage and also as uterine sedatives in disturbances of the menstrual function.

Quite recently **epinephrin** has been employed for its effects on the uterus (*Neu*). Its energetic oxytocic action has already been mentioned. On account of the readiness with which it undergoes change in the organism, neither its intrauterine nor hypodermic administration causes much rise of blood-pressure, but the small amounts which remain unchanged are sufficient, even after hypodermic administration, to excite or to strengthen the contractions of the very readily excited muscle-fibres of the gravid uterus. It may, therefore, be used subcutaneously for the induction of labor, to strengthen labor pains, or to check uterine hemorrhage.

After the birth of the child the use of this drug is free from danger, but clinical experience must decide whether, with careful dosage, its use during labor is unattended with risk of causing tonic contraction of the uterus with its peril to the child.

This drug has also been directly injected into the uterine muscle to check post-partum hemorrhage, and also during cæsarian section, both to render the uterus bloodless for a time, and to secure its maximal contraction.

According to still more recent observations, *extracts of the infundibular portion of the hypophysis* act like "a mild and under all conditions harmless epinephrin," which may be used in the same indications (*Foges* and *Hofstätter, Hofbauer, Neu*).

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CHAPTER VIII

PHARMACOLOGY OF THE CIRCULATION

FACTORS CONTROLLING THE CIRCULATION

Blood flow and blood-pressure are governed by three factors,—the quantity and quality (viscosity) of the blood, the work done by the heart, and the calibre of the vessels and their activity. The rapidity of the flow through the whole circulation depends on the reciprocal relationship of these factors. Directing our attention to the separate vascular systems, we may for the time being consider the work done by the heart and the volume of the blood as constant, while the third factor—that is, the state of contraction of the vessels—changes from moment to moment according to the needs of the various organs.

In general it may be said that, under physiological conditions, the more active an organ is the more blood will it contain, for, as everywhere in the body, the rule, that a physiological activity brings about conditions which favor its efficient accomplishment, holds good for the relationship between the activity of an organ and its blood supply. The demand creates a supply, so that the activity of an organ governs its blood supply.

This vasodilatation of active organs is brought about by reflexes causing inhibition of vasoconstriction as well as stimulation of vasodilators, and substances formed during the activity of the organ act locally on the vessel walls, causing local vasodilatation (*Gaskell, Loewi u. Henderson*).

The activity, or inactivity, of the various organs may bring about very marked changes in the distribution of the blood. The muscles of a rabbit at rest contain but 33.6 per cent. of the total blood, but this percentage is increased to 66 per cent. or more during violent muscular effort (*Ranke u. Spehl*). With the dilatation of so many vessels resulting from general muscular activity and the resultant decrease of the resistance, there would necessarily be a very marked fall in the general blood-pressure, and a slackening of the blood flow in other organs (*e.g.*, in the heart and central nervous system), were there not an efficient compensating mechanism to prevent this. The conditions which prevail during muscular activity show that there is ample provision for such compensation, for, as a matter of fact, blood-pressure actually rises during muscular activity (*Zuntz u. Tangl, Tiedemann, Krone*). This compensation is brought about not only by an increased efficiency of the heart function, but also by a narrowing of the vessels in other organs,—*e.g.*, the portal vessels, —which compensates for the dilatation of the vessels in the muscles. On the other hand, although during digestion the abdominal viscera are more richly supplied with blood, the other organs receive com-

paratively little, so that the aortic pressure is not necessarily lowered (*Pawlow*).

There is thus a continuous compensatory balance maintained between the different vascular systems, especially between the portal system and the peripheral vessels in the skin, muscles, and brain. This reciprocation between these two great systems is well illustrated when the depressor nerve is stimulated, there resulting a dilatation of the visceral vessels and a contraction of the peripheral ones (*Bayliss, Dastre et Morat*). On the other hand, stimulation of sensory nerves or of the splanchnics, or asphyxia, causes a vasoconstriction of the abdominal vessels and dilatation of most of the vessels of the skin, muscles, and brain. We find this same difference in behavior resulting from the administration of various drugs (epinephrin, digitalis, strychnine, and others). Other combinations are also possible,—for example, cold applied to the skin causes contraction of the cutaneous and renal vessels, while the other visceral vessels dilate (*Wertheimer, O. Müller*). Mental activity causes an increased blood supply to the brain and a lessened supply to the skin and muscles of the head and to the abdominal viscera (*Mosso, Weber*).

This regulation of the distribution of the blood is, in part, reflex in its mechanism. For instance, when the internal vessels are constricted, the vasodilatation in the extremities is partly the result of central nervous action (*Delezenne*), but it also results in part from a forcing out of the blood from the constricted vascular systems into others, the vessels of which are thus mechanically dilated. In certain vascular systems which are little, if at all, under vasomotor control, the changes in the blood supply are brought about entirely in the latter fashion.

Although we have but a limited knowledge of the details of the various compensatory regulations by which the different vascular systems maintain the equilibrium of the circulation, we know that disturbances of this compensatory mechanism play an important rôle in pathology. We know too that in the circulatory action of drugs the decisive factor is often the changed distribution of the blood and not the change in the aortic pressure. If, for any reason, in conditions in which the blood distribution is altered from the normal, this compensatory regulation does not occur, its mechanical results affect the whole circulation, including the heart itself.

This occurs when important and extensive vascular systems are relaxed and when compensation therefor does not occur. In such case the total amount of blood in the body is not sufficient to fill the relaxed vessels, for the total volume of blood is sufficient for the filling of the vascular systems only when the total cross-section of the vascular tree is equal to its normal mean, which mean is ordinarily maintained by the changing play of the vasomotor mechanism. Therefore, in conditions of vascular paresis, it is evident that the heart is unable to work efficiently, for, when the vascular system has lost its tone, the left heart pumps its blood not into an elastic system of tubes which

are able to deliver their contents back to the right heart, but it pours it out into a relaxed system in which the blood must stagnate to a greater or less extent. As a result the heart is insufficiently supplied with blood.

As shown above, uncompensated vasodilatation impairs the heart action, and the same is true when wide-spread vasoconstriction occurs. In the latter case, as a result of the increased peripheral resistance, the blood-pressure must rise greatly, and, if compensatory relaxation of other vessels does not occur to relieve the heart, the left ventricle may no longer be able to empty itself against the excessive pressure, and stasis of the blood in the heart results (*Tigerstedt*).

This short discussion has already shown how the activity and efficiency of the heart depend on the maintenance of a mean total cross-section of the vascular tree by the interplay of the different vascular systems (*Hensen*). Clinically, this is clearly evident, for, under different conditions of increased or diminished cardiac activity (tachycardia, fever, disturbance of compensation, etc.), causing marked variations in the blood flow, there may be no change in the radial blood-pressure, the vascular system by compensatory dilatation or contraction accommodating itself to the varying output of the heart. Ever since the observations of *Tappeiner* and *Worm-Müller,* it has been known that the blood-pressure quickly regains its former height even after extensive loss of blood, and it is under just these conditions that we may especially well observe this accommodation of the vascular system to varying states of fulness. Although after hemorrhage an inpouring of fluid from the lymph and tissues plays an important part in restoring the blood-pressure, its rapid re-establishment is chiefly due to the fact that the vessels throughout the body contract about their diminished blood contents. On the other hand, in artificial plethora the blood-pressure is raised only by very great overfilling of the vascular system, and even then but momentarily (*Cohnheim*).

The circulation is further protected from disturbance by another adaptive mechanism, which helps to maintain the proper equilibrium between the arterial and venous systems. If the blood is to be kept circulating normally, it is essential that during a given period the same quantity of blood must pass each total cross-section of the vascular tree,—that is, in a given period as much blood must enter the heart from the veins as leaves it to enter the arteries. If this balance be disturbed, the blood will accumulate in some portion of the circulatory system, most likely either in the heart itself or at the point where the arterioles and capillaries join with the veins. Epinephrin injections, by increasing the resistance in the arterioles, may cause an overfilling of the arterial portion, or a dilatation of the capillaries may cause an accumulation at this point with a resulting "capillary stasis," while insufficient cardiac activity may lead to an accumulation

of blood in the heart itself, in the pulmonary system, and in the great veins emptying into the heart,—"cardiac stasis."

Everywhere we see that disturbances of the heart function produce effects on the vascular system and that the changes in the vessels affect the cardiac function. With such reciprocal action of the separate factors and such mutual interdependence, it is evident that there can be no such thing as a pharmacological action affecting exclusively either the heart or the vessels, for, just as pathological alterations of the heart or vessels necessarily affect the whole circulation, so it is with those produced by pharmacological agents. Bearing these facts in mind, it is evident that, in the analysis of pharmacological actions of the various circulatory drugs, it is essential to determine their primary seat of action, as this often renders it possible to explain the whole combination of the phenomena resulting from their administration. Therefore the action of drugs on the heart and on the vessels will be discussed separately, while their effects on the circulation as a whole will be taken up later. Moreover, in any investigation of such drugs one should first of all endeavor to determine whether a drug acts primarily on the heart or on the vessels.

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METHODS OF INVESTIGATING THE CIRCULATION

The experimental pharmacology of the circulation started with the study of the changes in the aortic blood-pressure resulting from the administration of various drugs and poisons. The mean pressure in the aorta must furnish enough hydrostatic pressure to maintain a flow of blood through the various organs which will be sufficient properly to maintain their various functions. A decided fall in aortic pressure is, therefore, in itself a sign of marked disturbance throughout the circulation. As, however, the aortic pressure represents only a gross value resulting from the momentary efficiency of the

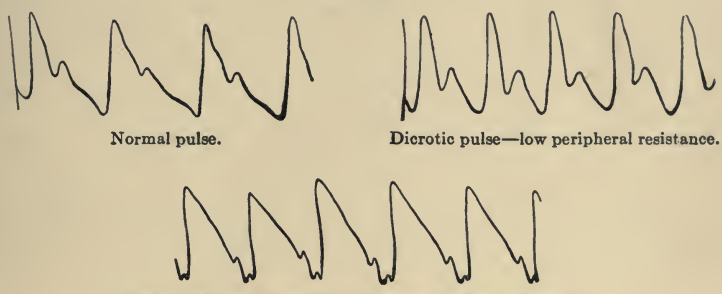
heart and the total vascular resistance, other supplementary methods are needed for the determination of the separate factors.

Before starting on a close analysis of the blood-pressure as studied in animal experimentation, it is proper to discuss briefly the methods used in the clinical observations of the circulation in man, for the more refined actions of drugs often stand out more sharply under pathological than under normal conditions.

CLINICAL METHODS

Sphygmograms.—Some deductions may be made as to the functional activity of the heart and the condition of the vessels from the graphic registration of the radial pulse. The form of the pulse wave—*i.e.*, the course of the pressure changes in the radial—is dependent, on the one hand, on the work done by the heart and, on the other, on the resistance in the vascular system (*O. Frank*). The sphygmo-

Fig. 17a.



Normal pulse. Dicrotic pulse—low peripheral resistance.

Tense pulse—high peripheral resistance (case of lead colic).

gram is altered from the normal by various pathological conditions, as, for example, in aortic insufficiency, by the fact that the blood leaves the arteries in both directions or that in arteriosclerosis it flows out but slowly from the inelastic vessels (*Sahli*). In a similar manner pharmacological agents may influence the form of the pulse-wave, should they change either the inflow into the aorta—*i.e.*, the "pulse volume" of the heart—or alter the rate of outflow into the capillaries by affecting the calibre of the vessels. With due allowance for technical difficulties, it may be stated, with reasonable certainty, that when the peripheral resistance is low the dicrotic wave will be well developed in the sphygmogram while the so-called "elasticity" elevations tend to disappear, while with increased peripheral resistance the opposite occurs (Fig. 17a). In spite of all uncertainty in the interpretation of sphygmographic curves, the position of the anacrotic wave high up on the ascending curve near its summit, a rounded summit or a plateau-like one, indicates high tension in the arteries.

Changes in the pulse tracings are frequently evident after the administration of drugs and poisons which influence the vessel calibre. Thus, during the attacks of spasmodic contraction of intestinal vessels which occur in lead colic, the pulse is that of high tension, with diminution or disappearance of the dicrotic wave and the presence of an anacrotic elevation. On the other hand, vasodilating drugs, such as chloral (in large doses), cause the pulse to resemble that of fever. During the treatment of vascular spasms by amyl nitrite, one may often observe the transition of the pulse from one form to another (Fig. 17b). In such case the change in the sphygmogram is much less the result of the vasomotor changes in the radial artery and its branches than of the alteration of the general vasomotor tone, which is the decisive factor for the whole circulation (*Sahli*).

THE CLINICAL DETERMINATION OF THE BLOOD-PRESSURE is of much greater significance for the pathology and pharmacology of the circulation. The technic of blood-pressure determination has in recent time reached such perfection that the maximal systolic pressure may be

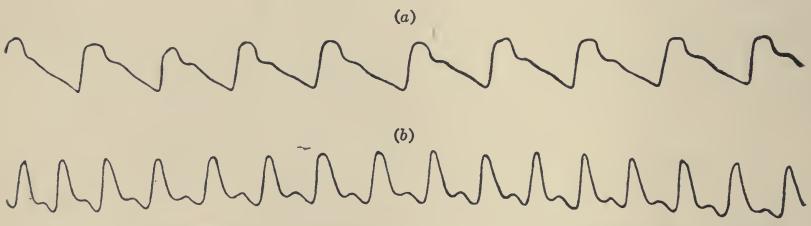


FIG. 17b.—Sphygmograms from case of lead colic: *a*, before, *b*, after inhalation of amyl nitrite.

determined with a high degree of accuracy, while the diastolic minimum may be approximately estimated.* From these two values one may determine the variation in pressure in the radial arteries (pulse-pressure) and its relation to the mean pressure. While the older methods of *v. Basch, Riva-Rocci, Gartner,* and others gave clinically valuable but only approximately correct values, *v. Recklinghausen's* modification of *Riva-Rocci's* method has a percentage of error of but 7 to 9 per cent. for the maximal pressure, as has been shown by the direct measurement of the brachial pressure in an arm just prior to amputation. The determination of the minimal diastolic pressure is more difficult, and up to the present time is attended by greater factors of error. [See footnote.—TR.]

The most important results obtained by clinical observations of blood-pressure have been the demonstration that a marked rise in blood-pressure often occurs in disease, but that, contrary to our former views, a marked fall in blood-pressure actually occurs much less frequently, and is observed, as a rule, only a short time before com-

* [By the auscultatory method both may be determined with quite sufficient accuracy.—TR.]

plete failure of the circulation. Even in cardiac decompensation, marked lowering of the blood-pressure is the exception, for the pressure is maintained near the normal level by compensatory vasoconstriction, and thus the best circulation possible is maintained in the vital organs. This regulation by the vessels so complicates blood-pressure conditions that the essential question, whether the primary seat of a pharmacological action be in the heart, vessels, or nervous system, can never be answered without further information than that obtained by the methods discussed above.

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EXPERIMENTAL METHODS

Only by closer analysis of the blood-pressure in experiments on animals can such information be obtained. Here methods may be used which are beyond criticism and which enable us to determine the causes of rise or fall in blood-pressure, at any rate for those grosser changes which are not compensated for by the regulatory mechanism.

A FALL IN THE AORTIC PRESSURE may be due to the lessened inflow of blood resulting from a diminished output by the heart, or it may result from a lessening of the resistance in the vessels. If a fall in pressure is caused by a general vasodilatation, then the blood-pressure will be re-established at its normal level if the total vascular cross-section be artificially diminished. This may be accomplished by clamping the aorta, which will cause the blood-pressure to return to its normal level if lessened resistance were the cause of the fall.

It having in this fashion been shown that the fall of blood-pressure was due to vasodilatation, it must further be determined if the loss of vessel tone is due to an interference with the central or the peripheral vasoconstrictor mechanism. Electric stimulation of the vasomotor centre in the cervical cord or of the vasomotor nerves—*e.g.*, the splanchnics—may then be employed to test the excitability of the peripheral mechanism.

In case a drug has caused a RISE OF BLOOD-PRESSURE as a result of a wide-spread vasoconstriction, it must similarly be determined whether this be due to stimulation of central or of the peripheral vasoconstrictor mechanisms. To decide this, the cervical cord may be cut and the effect on blood-pressure noted. To exclude action of the secondary vasomotor centres in the cord, this too may be destroyed by pithing. Centrally acting drugs, such as strychnine, will under these conditions no longer raise the blood-pressure. If, however, the drug still affects the blood-pressure in the aorta, it must act

peripherally—that is, in the vessel walls themselves. Substances of the digitalis group, epinephrin, and barium salts are examples of drugs which under the above conditions may still cause a marked rise of blood-pressure.

If the RELAXATION OF THE VESSELS is caused by depression of the vasomotor centres, the diminution in their excitability may be followed step by step if different stimulating agents be used. These centres first lose their reflexive excitability to stimulation through the sensory nerves, the blood-pressure failing to rise after stimulation of the sciatic. Chemical stimuli are the next to lose their effect, and therefore the blood of asphyxia, normally a vasoconstrictor stimulant, may be used as a means of testing their excitability. Finally, in complete paralysis of the vasomotor centres, even direct electric stimulation of the cervical cord is without effect.

If the vascular paresis be peripheral, it is self-evident not only that the above-mentioned stimulants of the vasomotor centres will produce no effect, but also that stimulation of vasomotor nerves will be ineffectual. If, for example, one is dealing with a peripherally induced paresis of the portal vessels, such as occurs in arsenic poisoning, the stimulation of the splanchnics will, as the poisoning develops, produce constantly diminishing effects.

Through such experiments it is possible to determine definitely whether or not the action in question is dependent or not on the central nervous system. We cannot, however, by these methods determine at all whether the changes in the blood-pressure result exclusively from peripherally caused changes in the calibre of the vessels, or whether they also in part arise from changes in the cardiac function. This may be decided beyond question only by a further analysis, during which the action on the heart and that on the vessels may be better differentiated.

Repeatedly attempts have been made to exclude the central vasomotor innervation and the peripheral mechanism by the use of large doses of depressing drugs, such as chloral hydrate or amyl nitrite, and then to test the action of blood-pressure-raising (pressor) substances. However, this method of experimentation is not free from sources of error, for the second drug may overcome the vascular paralysis and thus the deduction of a pure cardiac action be unjustified.

METHODS FOR STUDYING THE EFFECT OF DRUGS ON THE CARDIAC FUNCTION

If an effect on blood-pressure is not the result of changes in the calibre of the vessels, it has usually been concluded that it is due to a change in the work performed by the heart, and the endeavor has been made to supplement the analysis of the blood-pressure by experimentation on the isolated surviving heart. In addition, by the simultaneous graphic registration of the blood-pressure and of the functional activity of the heart by plethysmography of this organ or by similar methods, further data for the estimation of the activity

of the heart may be obtained. However, the real decisive factor, the pulse volume of the heart, may be exactly determined in the intact circulation only by measuring the amount of blood which the heart pumps out into the aorta. The measurement of the volume per minute, by the use of a *Tigerstedt's* " Stromuhr " placed in the aorta, has recently given results of much importance in connection with the study of the action of epinephrin, the digitalis group, etc.

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Observations on the isolated frog's heart have rendered to pharmacology invaluable service in the determination of the seat of action of drugs affecting the circulation, the classical material for such observations being the surviving frog's heart.

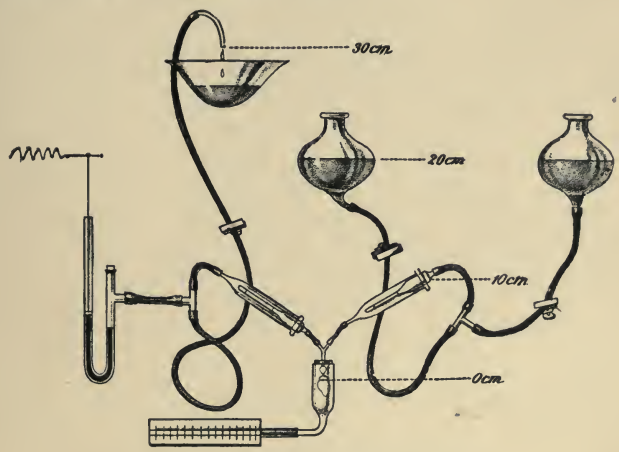

Fig. 18.—Williams's frog-heart apparatus.

In 1866 *Cyon*, in C. Ludwig's laboratory, was the first to conduct such experiments. Soon after this *W. Blasius* and *Böhm* used the same method in Fick's laboratory. At first the frog's heart was used with the sinus, auricles, and valves attached, the heart receiving the artificial nutrient solution (diluted blood, rabbit serum, or Ringer's solution) through one vena cava and expelling it through the aorta, the other veins and arteries having been ligated. The observation of the surviving frog's ventricle was further simplified by the use of *Kronecker's* frog-heart manometer, in the use of which a double cannula was introduced into the ventricle after removal of both sinus and auricle. *Straub's* simple method is for many purposes the best. In it the heart receives the nutrient solution through a simple funnel cannula from a column of fluid of a minimal height of 2–3 cm. By its own beats it keeps the fluid well mixed and may continue actively beating for hours.

For the pharmacologist **William's frog-heart apparatus** (Fig. 18) is the most useful. By means of artificial valves, which take the place

of the cardiac valves, the nutrient solution circulates in this apparatus through a rigid system of tubes under pressure conditions which may be altered at will.

Two glass reservoirs of about 30 c.c. capacity are used as containers for the normal solution and for the solution containing the drug. The rubber tubes from these are joined together by a Y-tube, through which either solution may be conducted through the valve of ingress to a double cannula which leads into the ventricle. The other branch of this cannula is connected with a second valve, which, like the aortic valve, keeps the solution from flowing back into the ventricle but permits it to return to the reservoir. A manometer is connected to that part of the system which represents the arterial system. By narrowing or widening the point of exit from this system, the pressure may be varied at will in this tube which represents the aorta.

As soon as the necessary resistance is produced, each heart-beat causes a certain rise in pressure in the manometer. If this resistance to the outflow be kept constant, a change of the mean pressure or in the size of the pulse in the fixed system of tubes can be the result only of a change in the functional activity of the heart. With this apparatus the pulse volume of the heart may be determined either by measurement of the fluid pumped out or by plethysmographically recording the changes in volume between the systolic and diastolic phases of the ventricle. The work done by the heart may at any time be calculated either for the unit of time or for the individual heart-beat, for the work done is the product of the amount pumped out, the pulse volume, multiplied by the pressure against which the heart empties itself. If this pressure be increased by raising the outflow point, a pressure may be reached which the heart is no longer able to overcome. Thus the absolute power or strength of the heart is determined (*Dreser*).

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Experiments on the Isolated Mammalian Heart.—By perfusing its coronary vessels the isolated mammalian heart may also be kept beating for hours. By this method, too, or by the method of *Hering* and *Bock* (see below), it is possible to study the action of drugs on the heart while excluding any actions on the general vascular system.

The method of *Hering* and *Bock* (Fig. 19) is as follows:

The descending aorta and both subclavians of a rabbit are ligated. One carotid having been connected with a manometer, from the other the blood passes through a U-tube into the jugular vein. The pulmonary vessels are left undisturbed, and the blood passing through the lungs is arterialized and enters the left heart. It then passes through the aorta into the carotid, through the glass tube into the jugular, through which it then flows back into the right heart. The glass tube thus replaces the general vascular system, but in it the resistance remains constant. The pulmonary circulation is not disturbed, but this may be disregarded, for *the pulmonary vessels are little or not at all affected even by the most powerful vasoconstricting or vasodilating drugs* (*Gerhardt*). The vascular system under these conditions is thus represented by a system of tubes, which with the exception of the coronary vessels must maintain a constant resistance.

The heart is physiologically isolated, so that any change in blood-pressure in this system must be the result of an alteration in the cardiac function.

The method of perfusion of the surviving mammalian heart, chiefly developed by *Langendorff,* depends on a fact already observed by *Ludwig,* who found that even an isolated mammalian heart may survive and continue to beat if the coronary vessels be perfused at body temperature with defibrinated blood or other appropriate nutrient solutions. Under such conditions a heart may continue to beat for hours if kept in a moist chamber and under proper conditions.

Langendorff causes the blood to flow into the aorta under pressure, and, as the aortic valve remains closed, the only outlet for the blood is through the coronary vessels, from which it flows into the right auricle, leaving the heart here. The cavities of the heart remain empty, but the heart beats for long periods with satisfactory regularity if the supply to the coronary vessels is suffi-

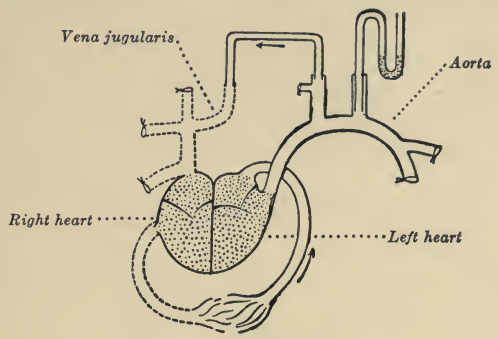

Fig. 19.

cient and constant and if the temperature be maintained constantly at the right degree. If these conditions be maintained, any changes in the action of the heart may be attributed to the drug which is perfused. A heart perfused according to this method preserves a fairly normal excitability of both its muscular and nervous elements, so that it will respond to both vagus and accelerator stimulation (*Langendorff, Hering, Steinberg*).

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METHODS FOR STUDYING PHARMACOLOGICAL ACTIONS ON THE VESSELS

The pharmacological investigation of surviving vessels is also feasible, for the vessels of organs removed from the body and properly perfused with appropriate solutions at body temperature also "sur-

vive'' for a considerable period. If the perfused fluid be allowed to flow under constant pressure through the arteries of such organs as the kidney, spleen, or an extremity, and the amount flowing out in a unit of time be noted, any increase or diminution in the rate of flow can be due only to a change in the calibre of the vessels, the cause of which must lie in the vessel walls themselves.

Mosso, in Ludwig's laboratory, making use of the method of perfusion, was the first to demonstrate the peripheral action of a drug on the vessel walls. It must, however, not be forgotten that surviving vessels are no longer under physiological conditions, even when perfused with defibrinated blood, which is so especially suitable for the maintenance of the chemical processes in the tissues, for the blood never flows through a surviving organ so rapidly as it would in the living animal under like conditions of pressure and inflow, and its rate of outflow diminishes progressively with the lapse of time. Moreover, even slight variation in the composition of the artificial nutrient solution from that of normal blood—for example, the defibrinization—is of moment here. The method is thus necessarily one attended by many sources of error. Perfusion with blood-free Ringer's solution gives the most constant results.

Recently a new experimental method has been devised which permits of the direct observation of changes in the tone of excised circular strips of the arteries. By proper treatment in Ringer's solution maintained at body temperature, isolated vessels may be maintained for days in an excitable condition, so that drugs acting peripherally will exert their specific action on such material (*v. Frey, J. B. Meyer, Langendorff*).

The peripheral actions on the vessels are, however, in no way alone responsible for the behavior of the different vascular systems in the living body, where they are under the influence of the central nervous system and, as previously stated, are often influenced by various compensatory regulations. Other methods (*F. Pick, Biedl, Barcroft* and *Brodie*) are, therefore, needed which will permit the determination *intra vitam* of the blood flow through the different organs, in order that we may determine the rôle played by the various vascular systems in the circulatory changes taking place throughout the body. Here observations of the outflow from veins and plethysmography are of value.

A plethysmogram shows the changes in volume taking place in an organ enclosed, with its afferent and efferent vessels, in an air-tight container constructed especially for this purpose. *Roy*, using his oncometer, was the first to measure the volume changes of the kidney, but at the present time *Schaefer's* plethysmographs are usually used. If the container is connected with an apparatus for registering changes of volume, such as the piston recorder, the separate pulse-waves are visible, the increase of volume of the organ caused by each heart-beat driving air out of the oncometer. In the same fashion the volume of the enclosed organ follows the changes in blood-pressure during longer periods, the vessel being passively dilated by increased blood-pressure or less completely filled as the pressure falls.

Thus, the plethysmographic curve moves in the same direction as the blood-pressure curve if the vessels in the enclosed organ are not themselves influenced by the drug employed. If these vessels, however, are contracted, the volume of the organ does not increase, but, on the contrary, diminishes, as the blood-pressure rises, and the two curves move in opposite directions; while, on the other hand, if the enclosed vessels actively dilate, the plethysmographic curve rises, although the blood-pressure remains constant or even if it falls, and thus this curve may cross the blood-pressure curve. In Fig. 20 is seen a plethysmographic curve obtained from a loop of gut enclosed in a plethysmograph. This shows the changes in the volume of the intestines during stimulation of the splanchnic nerve. This method, as also the outflow method, permits of the simultaneous determination of the blood flow through several organs and of their influence on each other. Pharmacological vasomotor actions may also be analyzed after section of the vasomotor nerves, and in such experiments electric stimulation of these nerves is often employed.

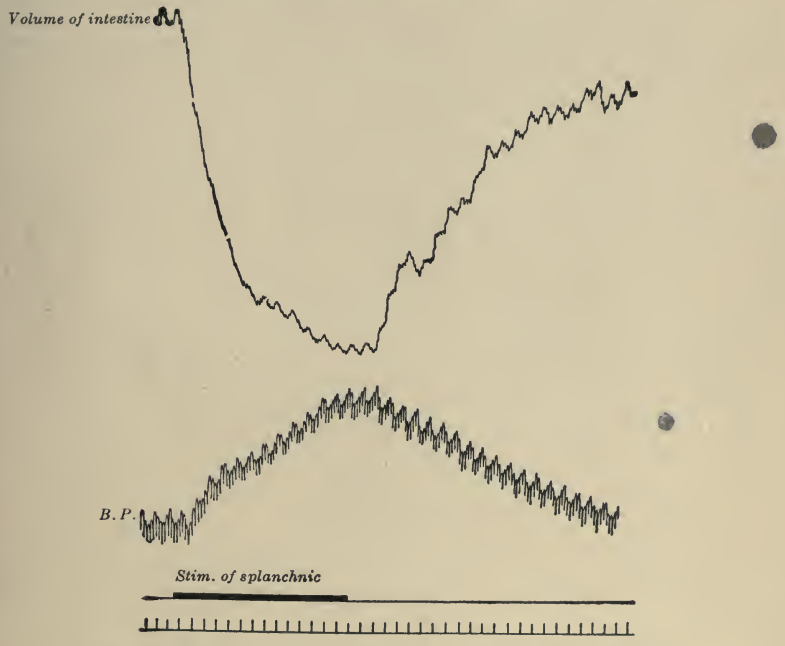

Fig. 20.—Effect on intestine of stimulation of the splanchnic (*Lehndorff*).

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PHARMACOLOGY OF THE HEART

All the factors necessary to its activity are contained within the heart itself. Normally the stimuli for the automatic cardiac movements in the frog's heart originate in the sinus venosus, and in the mammalian heart at the mouth of the great veins (*Adam*), the rhythm of the heart being normally determined at these points,—that is, the motor stimuli for the heart are here transformed into rhythmic stimuli (*Gaskill* and *Engelmann*). The function of these motor centres in the heart may be variously influenced by drugs and poisons.

A brief explanation of the frequently observed vital phenomenon known as rhythm (*Steinach*) may aid in our understanding of these points. One of the comparatively few established and fundamental properties of all nervous centres (either ganglia or nerve-plexuses) is their power to summate continually arriving stimuli and thus to make them effective. After a certain period this summation results in a discharge of energy from the nervous organ, which is succeeded by a phase of exhaustion, during which the centres remain refractory—that is, insusceptible to stimulation—until sufficient energy has again been developed in them, catabolic and anabolic processes thus alternating. This periodicity of function in the centres has as its visible effect the periodic activity of the organs under their control,—*e.g.*, the respiratory muscles, the heart, etc. For such centres as are normally constantly called upon, this refractory phase is a vital necessity, enabling them to develop again the energy needed.

The fundamental work of *Gaskell* and *Engelmann* has demonstrated that in the study of cardiac activity we must differentiate between the different cardiac functions which are involved, as these may be separately affected by different pharmacological agents. The frequency with which stimuli pass to other portions of the heart is normally controlled by the state of the stimulus-producing mechanism in the sinus (chronotropic or retarding influence of the sinus). This mechanism determines the rhythmic activity of the heart, which is the first of its physiological characteristics to be considered.

It may further be shown that such stimulus-inaugurating mechanisms exist not only at the situations mentioned but also in all parts of the heart. However, the automatism of the lower portions of the heart is only latent,—that is, it remains inactive as long as the controlling mechanism in the sinus is active and inhibits these secondary ones. This is analogous to the phenomena of intracentral inhibition in the central nervous system.

The functional activity of the ventricles is controlled and may be pharmacologically influenced by the following factors:

1. *The power of rhythmical activity of the stimulus-producing mechanism in the sinus,—chronotropic function.*
2. *The rate of conduction of stimuli in the heart,—dromotropic function.*
3. *The functional capacity of the excitable peripheral motor mechanism in the heart (nerves or muscles),—bathmotropic function.*
4. *The momentary internal condition of the heart muscle, which alone, quite independently of the strength of the stimulus, determines the extent and power of the contraction,—inotropic function.*

All these different functional attributes of the heart are susceptible of influence through both the extracardial and the intracardiac nerves, the heart receiving from the central nervous system a double nerve supply, the inhibitory vagus from the cranial autonomic parasympathetic system and the accelerator fibres from the sympathetic system. Both nerves may be acted upon by drugs at their points of origin in the central nervous system as well as peripherally in the heart.

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PHARMACOLOGICAL ACTIONS ON THE EXTRACARDIAL NERVES

THE INHIBITORY CENTRE IN THE MEDULLA is directly stimulated by a number of agents, the best-known example of this being its stimulation by the blood of asphyxia. Certain medullary convulsants (*Krampfgifte*), such as picrotoxin and cicutoxin, like asphyxia, simultaneously stimulate the vagus and the vasomotor centres (*Böhm*). Epinephrin (*Verworn, Biedl u. Reiner*) and the digitalis group (*Kochmann*) also directly stimulate the vagus centre independently of their indirect actions on it. However, in the case of those substances which cause a rise in blood-pressure, as also in asphyxia, it is extremely difficult to distinguish between a direct stimulation of the vagus centre and an indirect stimulation resulting from the rise in blood-pressure.

As shown by *Bernstein,* the tone of the vagus centre depends on the height of the blood-pressure, it being augmented by a rise in blood-pressure, such as that caused by a temporary overfilling of the arterial system, while during a fall in blood-pressure, such as follows hemorrhage, the pulse becomes more rapid, the vagus centre being rendered less susceptible to reflex influences. It therefore follows that *the rate of the heart is altered secondarily by all pharmacological agents which raise or lower the general blood-pressure.* Thus, the pulse is slowed by the rise in blood-pressure produced by strychnine and accelerated by the fall caused by amyl nitrite, although these drugs have no direct action on the vagus centre.

As is well known, section of the vagi is followed by more or less pronounced acceleration of the pulse, this being due to the abolition of the restraining influence of this centre, and varying in intensity according to the species of animal in question. It is self-evident that after section of the vagi there can be no slowing of the pulse through any stimulation of this centre by drugs or other agents. Paralysis of the vagus centre by drugs or poisons produces the same results as section of the nerves, and causes a corresponding acceleration of the pulse, which varies in extent with the animal observed.

Acceleration of the pulse may also be due to *stimulation of the accelerator centres.*

The acceleration of the pulse preceding vomiting is an example of the effect of such accelerator-centre stimulation. Further, the blood of asphyxia stimulates this centre just as it does the vagus centre. Therefore, asphyxia of a curarized animal causes acceleration of the pulse if the vagus has been eliminated by section or otherwise (*Dastre et Morat, Konow u. Stenbeck*). So long as the vagus is functioning, the effect of its stimulation outweighs that of the accelerator stimulation, just as normally the vagus tonus is more powerful than that of the accelerator (*Hering*). It is probable that a central accelerator stimulation is in part responsible for the acceleration of the pulse which follows the primary slowing caused by the medullary stimulants, picrotoxin and cicutoxin (*Böhm*).

The peripheral actions of drugs on the vagus and the accelerator are readily comprehensible if we consider the general principles of pharmacological action on the vegetative nervous system. In accordance with these general principles, it is to be expected that the inhibitory mechanism will be influenced by those agents which also act on the other autonomic nerves, and that the accelerator will be influenced by those affecting the sympathetic system. In both vegetative systems the seat of action may be in either the nerve-endings or the intermediate ganglia.

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Drugs Acting on the Vagus in the Periphery.—The same drugs, whose specific action on the autonomic nerves has already been learned in connection with their action on the intestines, have been found to have similar pharmacological actions on the peripheral portion of the cardiac vagus, which, as we know, belongs to the cranial autonomic system. Thus, it is known of *nicotine* that it for a time stimulates and then depresses the ganglia interposed in the path of the autonomic fibres. This is the explanation of that peculiar action on the inhibitory cardiac nerves which was first explained by *Schmiedeberg*.

Action of Nicotine on the Frog's Heart.—If a small amount of nicotine be administered to a frog, the heart action is soon slowed, in fact it quickly comes to a rest in diastole. This stoppage lasts at the most not more than one or two minutes, and soon the heart beats again, apparently just like a normal one. However, in this secondary stage the inhibitory mechanism behaves in a peculiar fashion, for if the vagus nerve trunk be stimulated no slowing occurs. If now the sinus be stimulated or muscarine be applied to the heart, it quickly stops in diastole and remains quiet. The nicotinized heart thus reacts to mus-

carine or to sinus stimulation like the normal organ, but to vagus stimulation like an atropinized one. The action of the nicotine must, therefore, have impaired the conductivity of some part of the inhibitory mechanism, a part through which the effective vagus stimulation must pass but which lies farther from the heart than the point at which sinus stimulation or muscarine acts. This portion has been named by *Schmiedeberg* the "intermediate portion" (Zwischenstück). According to the general laws which have been demonstrated by *Langley* and *Dickinson* for the action of nicotine on the autonomic ganglia, it may be concluded that the ganglia interposed in the vagus fibres lie between the vagus trunk and its nerve-endings.

The vagus trunk contains the preganglionic fibres, the stimulation of which, according to the rule, is ineffectual after administration of nicotine. Stimulation of the sinus affects the post-ganglionic fibres, whose nerve-endings are acted upon by atropine and muscarine but not by nicotine.

The stellate ganglion is, as it were, a relay station for the accelerator fibres, for, after administration of nicotine, the post-ganglionic accelerator fibres —which, in the frog and in some of the higher species, pass down in the vagus trunk—remain excitable, and, therefore, stimulation of the vagus still causes an acceleration of the pulse even after nicotine has been administered (*Schmiedeberg*).

Tobacco Poisoning.—In man, too, the pulse is unusually rapid in nicotine poisoning, this being due to prevention of the central vagus inhibition, as described above. Later the pulse becomes slower as a consequence of the depressing action of nicotine on the automatic motor mechanism of the heart. In chronic tobacco poisoning, irregular intermittent heart action is frequently observed. Acute tobacco poisoning is, however, not an effect of nicotine alone, for pyridine and a number of other toxic substances also play a rôle in producing the effects caused by smoking. The primary slowing and later the acceleration of the pulse, the increase of secretions and the increased peristalsis, with nausea and vomiting, may, however, be considered as due to the nicotine. The same is true of the pallor and faintness which are due to central depression.

Pilocarpine acts in a similar way on the "intermediate portion" of the cardiac inhibitory mechanism, causing, in the frog, slower heart action and diastolic standstill, which may last for as long as two minutes, and is then followed by more rapid heart action (*Harnack u. H. Meyer*). At this stage stimulation of the vagus is ineffectual, but direct stimulation of the sinus or application of muscarine to it results in a stoppage of the heart. With the higher experimental animals the stage of slowing passes even more rapidly.

Curare and many other drugs have a similar action on these autonomic ganglia, but such effects are produced only by large doses (*Langley* and *Anderson*).

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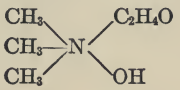
Muscarine and atropine act on the ultimate terminations of the vagus (cranial autonomic nerve).

Muscarine is an alkaloid obtained from one of the common poisonous mushrooms, Amanita muscaria, or Agaricus muscarius, or fly mushroom. It was first isolated by *Schmiedeberg* in 1868. These mushrooms also contain a much less poisonous base, choline (*Harnack*), which is formed by the decomposition of lecithine and which is a constant constituent of many animal tissues, and is chemically designated trimethyloxyethyl ammonium hydroxide,



Muscarine differs from this in its composition only by containing one more atom of oxygen, and is probably formed from choline by oxidation.

In fact, by allowing fuming nitric acid to act on choline, *Schmeideberg* and *Harnack* prepared an artificial muscarine, which, although similar to, is not identical with the muscarine obtained from the fly mushrooms (*Böhm, H. Meyer*). Its pharmacological actions, while resembling those of the natural alkaloid, are not entirely the same, for, although the action on the vagus nerve-endings is the same, it, on the other hand, causes paralytic phenomena resembling those resulting from the administration of curare.

Choline also has a pronounced muscarine-like action on the vagus nerve-endings, a fact which may be of some physiological significance, inasmuch as it has recently been shown that choline is a constant constituent of many tissues. It may well be that the variable amounts present under different conditions may exert an influence on the activity of the vagus nerve-endings.

Muscarine on the Frog's Heart.—If a small amount of muscarine be injected into a frog, the heart promptly begins to beat more and more slowly, and finally stands still in a state of maximal diastolic relaxation, the auricles usually stopping first. This is not due to a paralysis of the heart, for any mechanical or electrical stimulation of the ventricle causes a prompt contraction. In fact, the heart is more susceptible to such stimuli than is normally the case at the end of the usual short diastole. The excitability of the motor centres and the power of the muscles to contract are both preserved, although inhibited. The antagonistic action of atropine shows us the seat of action of this peculiar pharmacological effect. It has long been known that stimulation of the cervical vagus is ineffectual after small doses of atropine (*v. Bezold, Schmiedeberg*). Similarly muscarine no longer causes a slowing or stopping of the heart if atropine has been previously applied.

In the frog's heart muscarine produces the same effect as a continuous vagus stimulation. By the electric stimulation of the inhibitory fibres, the number of beats is lessened, the systolic contractions are rendered less complete, and the diastolic distention is increased. In certain cases the number of beats is markedly lessened, the pulse

volume of the heart remaining about normal, while in other cases the heart rate is little affected but the systolic contractions become very incomplete. While this holds true for the effects of small doses of muscarine (*Cushny*), with larger doses the heart rate is always markedly slowed and the diastolic relaxation strikingly augmented, or else the heart remains permanently relaxed. Muscarine, like vagus stimulation, is thus seen to be negatively chronotropic (retarding) and negatively inotropic (weakening).

If the heart of a cold-blooded animal be perfused with a solution containing muscarine, the typical slowing and stoppage result, but after a time the heart begins to beat again, although at this period the heart contains enough muscarine to stop another heart. If, after the heart has begun to beat again, still more muscarine be added to the perfused fluid, the same succession of events occurs, the heart stopping once more, but after a time beginning to beat again. It is thus evident that it is not the presence in the heart of a certain amount of muscarine which excites the inhibitory mechanism, but that the stimulus to the inhibition is caused by the process of permeation, the muscarine "pressure" (Gefälle) (*Straub*). In the case of other pharmacological actions on the heart—for example, that of the digitalis group—the effective factor is not the pressure produced during permeation, but is their combination with specifically susceptible elements,—that is, an alteration of physiological conditions.

Loewi has shown that the negative inotropic effects of muscarine may be promptly overcome by calcium salts, while all of its effects are promptly suppressed by the smallest doses of atropine, so that the heart beats like a normal one, and previous application of atropine prevents the development of any muscarine action.

While a complete suppression of the muscarine action may be effected only by the use of atropine, a number of substances which stimulate the cardiac motor mechanism cause the diastolic standstill to be interrupted by more or less frequent beats. While atropine abolishes all the characteristic changes in function produced by muscarine, the diastolic character of the heart action persists after the incomplete antagonistic effects resulting from the action of these other substances, the inhibition continuing, but being interrupted from time to time on account of the increased excitation of the motor elements. In this way a muscarinized heart may be used as a means of testing a stimulating effect due to action on the motor elements.

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Atropine.—Small doses of atropine have as their sole cardiac action that of depressing those vagal nerve-endings which are stimulated by muscarine. According to *Harnack* and *Hafemann*, 1/50 mg.

to 50 cm. of perfusion fluid is sufficient to produce this result, so that it is then impossible to cause inhibition of the heart by either vagus or sinus stimulation, or by muscarine, nicotine, or pilocarpine. In other respects the heart behaves normally. The following curve shows the effects of small doses of atropine in overcoming the muscarine standstill of the frog's heart, suspended according to the method of *Gaskell* and *Englemann:*

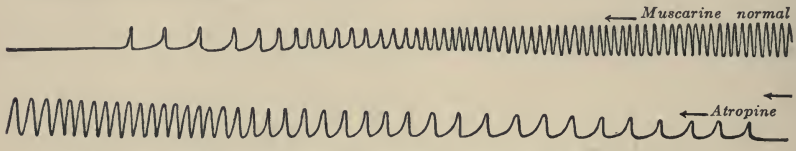

Fig 21.—Suppression of the muscarine standstill by atropine. Read from right to left.

In addition to their depressing action on the inhibitory mechanism, larger doses of atropine would appear also to exert stimulating effects on the motor mechanism of the heart. In *Langendorff's* experiments, atropine exerted a positively chronotropic influence on the secondary automatic motor centres which lie in the apex of the frog's heart. After functional separation from the higher controlling centres by clamping, the apex under ordinary conditions remains inactive. After application of atropine, however, contractions of the apex may occur spontaneously, or a mechanical stimulus causes a long series of beats, although an unatropinized apex responds to each stimulus with but one contraction. We are dealing here with an exciting action of atropine in doses which are many times larger than those which completely paralyze the inhibitory apparatus (*Hedbom*). The often-claimed suppression, by such larger doses, of the standstill of the heart, due not to inhibition, but to paralysis of the motor mechanism (*Luchsinger*), does not affect the value which small doses of atropine possess as a certain test for inhibitory actions. A standstill of the heart or a slowing of the pulse which is removed by small doses of atropine is due to inhibition.

The stimulation of the cardiac inhibitory mechanism by muscarine and its depression by atropine occur also in the mammal, in a fashion quite analogous to the above-described effects on the frog's heart. Stoppage of the heart or an extreme slowing of the pulse by muscarine necessarily, however, causes much more violent symptoms in the warm-blooded animal, on account of the secondary effects resulting from disturbed circulation. After a muscarine injection the aortic pressure sinks rapidly (Fig. 22). During the longer or shorter diastolic pauses the heart is maximally distended, only incomplete contractions interrupting the standstill. Inasmuch as the blood cannot pass from the greater veins into the overfilled auricles, the blood accumulates in the pulmonary system, and dyspnœa must quickly result, for the overfilling of the pulmonary vessels interferes with the air-change and at the same time the circular muscles are tonically contracted. The asphyxia must quickly prove fatal if a dose of atropine does not relieve it. Atropine may also overcome the marked pulse slowing, and if the heart has not been too much harmed by the asphyxia it quickly recovers. Previous section of the vagi causes no alteration in the phenomena resulting from the administration of the muscarine.

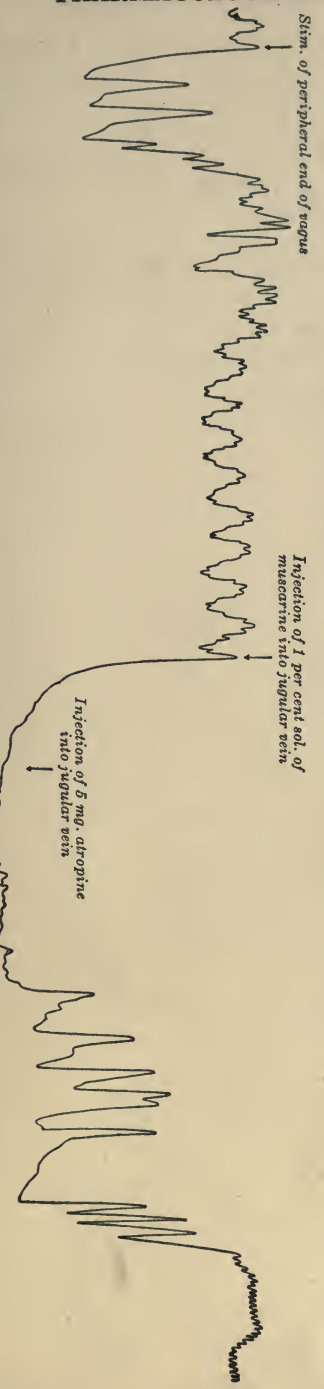

FIG. 22.—Circulatory action of muscarine in the mammal.

Of importance in connection with the poisoning produced by the fly mushrooms is a base resembling atropine (*Schmiedeberg*), as well as another poison still imperfectly investigated, which produces symptoms of excitation of the central nervous system and which is found chiefly in the fresh mushrooms (*Harmsen*). [A glucoside studied by *Ford* and *Abel* and possessing many interesting properties would appear also to be of considerable importance in this connection.—TR.] As a result of the combined action of these different poisons, the symptoms of mushroom poisoning differed markedly from those observed in poisoning by pure muscarine in the animals.

Muscarine Poisoning.—The symptom complex of muscarine poisoning results from its actions on the stomach and intestines, already described in a previous section, and from those on the eye and on the secretions, and especially from the actions on the circulation which threaten the life of the victim. It is especially well developed in the cat. The first symptoms—namely, chewing and licking movements, with flow of saliva—develop within a few minutes after the subcutaneous injection of several milligrammes. Active peristalsis, retching, vomiting, defecation, and tenesmus ensue, as well as contraction of the pupil, leading perhaps to its complete disappearance. The pulse becomes extremely slow, marked dyspnœa develops, and the animal can no longer maintain the upright position, but falls on its side, death with light convulsions resulting from stoppage of the respiration at a time when occasional heart-beats still occur. Atropine may rescue the animal, even in extremis, and this drug is probably the proper antidote in mushroom poisoning in man, as well as in poisoning by certain little-known ptomaines formed during putrefaction, which have a muscarine-like action.

PHYSOSTIGMINE. — During our study of the action of physostigmine on the intestines and on the pupils, we have learned that it is a drug which stimulates vagus nerve-endings

(*Winterberg*) and slows the pulse. As this effect is not completely suppressed by atropine, it follows that physostigmine must act on the heart at a different point from atropine, but the situation of this point has not yet been definitely determined (*Winterberg, E. Harnack*).

Actions on the Accelerator in the Periphery.—The nerve-endings of the accelerator nerves are part of the sympathetic system, and, like all the nerve-endings of this system, they too are stimulated by epinephrin. Cocaine's similar behavior toward the sympathetic system has already been discussed, and the acceleration of the pulse at the commencement of the cocaine action has been recognized as a side action of this drug. The influence of epinephrin on the intracardiac accelerator nerve-endings appears clearly in the isolated heart prepared according to Langendorff's method. Its effects on the intact circulation are complicated by the retardation of the pulse resulting from the already-mentioned stimulation of the vagus centre. In fact, at the start this slowing preponderates.

The increase in pulse-rate after the administration of caffeine or theobromine is also due to excitation of the accelerator nerve-endings. This may be seen in susceptible individuals after drinking strong coffee.

It may further be stated that it is not possible to differentiate between actions on the accelerator nerve-endings and the alterations in function of those mechanisms in the heart which we have defined as the "stimulus-producing mechanisms," and which from now on will, in the interest of brevity, be spoken of as the "motor centres." These centres in the heart are either identical with the accelerator nerve-endings—*H. E. Hering* was able by stimulation of the accelerator to cause the dog's heart, perfused according to *Langendorff*, again to beat automatically after it had entirely ceased to beat—or at least we are unable at present to distinguish between the accelerator nerve-endings and the motor apparatus of the heart. For these reasons the above-discussed pharmacological actions on the terminal portions of the accelerator nerves must also be considered as actions on the motor centres of the heart.

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CARDIAC DEPRESSANTS

The number of these is legion. In them are included, among others, the narcotics of the aliphatic series, of which those containing halogen are distinctly more harmful to the heart than those containing no

halogens. Using the isolated frog's heart, *Dieballa* has investigated quantitatively the activity of the different members of this group, and has ascertained that chloroform exceeds in its heart-depressing action all the other members of this group which were investigated. In order to produce the same cardiac effects as produced by chloroform, it is necessary to use of ethyl bromide 12 times the molecular concentration, of ether 48 times, and of alcohol 132 times. *Bock's* experiments with the "heart-lung-circulation" resulted in an equally indisputable demonstration of the enormous difference in the toxicity for the heart of chloroform and ether.

Numerous other substances belonging to different pharmacological groups have a similar power of causing retardation of the pulse and depression of the heart, which results finally in stoppage of the heart in diastole. According to *Brandenburg,* the salts of the bile acids must be included here, although these slow the heart also through action on the vagus centres (*Loewi, Weintraud*). With more pronounced pharmacological action, however, they directly affect the production of stimuli in the heart. This is of importance in connection with the slowing of the pulse in icterus, as this must be attributed to their direct cardiac depressant action as well as to the central stimulation of the vagus produced by them. Atropine usually overcomes the pulse-slowing in icterus, as was demonstrated by *Weintraud* in a series of cases. This, however, does not exclude the possibility that a depression of the motor apparatus, which is not influenced by atropine, may occur clinically as a second component of the toxic action resulting from the presence in the blood of larger amounts of these salts, just as is the case when either the frog's or the isolated mammalian heart is poisoned by larger doses.

With the aid of atropine it is possible to distinguish between pulse-slowing due to stimulation of the inhibitory mechanism and that resulting from depression of the motor mechanism. On the other hand, it is much more difficult to differentiate between a depression of the automatic motor centres in the heart and a depression of the contractile power of the cardiac muscles. Negative chronotropic and negative inotropic pharmacological actions usually go together, and soon after the cessation of its automatic activity the heart loses its excitability to mechanical, electrical, and chemical stimuli. This is the case, for example, after large amounts of quinine (*Santesson*). The potassium salts are also typical cardiac depressants if under certain conditions (intravenous injections or subcutaneous administration of very large quantities) their concentration in the blood is increased beyond 0.08 per cent. (*Tetens*). In this case, too, loss of excitability of the muscles follows quickly on the cessation of contractions.

Chloral hydrate is a type of the cardiac depressants. Under its influence the heart beats slower and slower, and during its prolonged diastole is more relaxed and distended than normally. Shortly after

stoppage in diastole has occurred, each mechanical, chemical, or electrical stimulus results in a contraction, but atropine does not overcome this standstill. In their physiological analysis of this progressive pulse-slowing, *Harnack* and *Witkowski* were able to determine that the seat of action of the paralysis lay in the automatic mechanism of the heart, for the rate of the whole heart was slowed by painting the sinus with chloral or the similarly acting iodal. Later a depression of the power of contraction also occurred. It is thus seen that the *primary action of chloral hydrate is negatively chronotropic, and, more weakly and usually somewhat later, it is also negatively inotropic.* The excitability and the conduction of stimuli are less affected (*Böhme*), and it may in general be said that *all these depressants mentioned influence the inotropic properties* (*contractility*), *the bathmotropic* (*irritability*), *and the dromotropic* (*conductivity of stimuli*) *functions qualitatively alike, but quantitatively in different degrees, while their effects on the chronotropic function* (*production of stimuli*) *follow special rules.*

There can be no doubt that there exist in the heart special mechanisms for the production of stimuli, and that these mechanisms may be affected by specific pharmacological actions. It makes no difference whether this function is attributed, in accordance with the neurogenic hypothesis, to nervous elements or to a special type of muscle-cells, as demanded by the myogenic hypothesis. All the characteristic functional properties of the cardiac muscle are found also in the apex of the heart, in which under usual conditions the capacity for the inauguration of stimuli is lacking, and which, therefore, under normal conditions remains at rest when, by clamping, it is physiologically isolated from the upper portion of the heart. However, it contains a mechanism for the conduction of stimuli, for an artificial stimulus at any point causes a simultaneous contraction throughout its whole extent. It also has a refractory period, and in the apex, just as in the intact heart, the strength of the contraction is independent of the intensity of any stimulus strong enough to be effective. Chloral hydrate almost completely abolishes these characteristic functions of the apex, while its susceptibility to single electrical stimuli as well as the function of conduction of stimuli persists, so that the heart apex still contracts as a whole after each efficient minimal stimulus. Inasmuch as the power of inaugurating stimuli is paralyzed throughout the whole heart simultaneously with these effects on the characteristic attributes of the cardiac function, the heart under these conditions resembles in its behavior a portion of intestine (*Magnus*) or a Limulus heart (*Carlson*), whose nervous motor centres have been anatomically separated from the muscles. In analogy with the above-mentioned examples, there is ground for concluding that by the use of chloral hydrate, a drug that in general paralyzes nervous centres sooner than nerve-fibres and muscles, we have succeeded in functionally eliminating those physiological properties of the heart, which are dependent on nervous centres or ganglia (*Rohde*).

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CARDIAC STIMULANTS

Stimulation of the motor mechanism of the heart is of the greatest therapeutic importance, for narcotic poisons or the toxins of infection may and frequently do functionally depress the heart to such an extent that a collapse of cardiac origin develops. In such case it is important to help the heart over a temporary period of inefficiency, as, if under the influence of a stimulant it beats better for even a short time, thus bringing about a higher pressure in the aorta, its own nutrition is improved, and it may thus be enabled to escape the death threatened by the poisoning.

Camphor.—In the pathological disturbances spoken of as acute failure, camphor is the stimulant most used, although on the normal heart the favorable action of camphor cannot be demonstrated with certainty. While it is true that a strengthening of the beats of a strongly beating frog's heart may be observed (*Heubner, Baum, Maki*) if the dose has, by good fortune, been properly determined, often such effect is not apparent (*Alexander-Levin*). Moreover, only in certain cases does camphor produce an improvement in function in the cat's heart perfused according to Langendorff's method (*Seligmann*). On the other hand, in pathologically weakened hearts it proves itself in incontrovertible fashion to be a stimulant to the automatic motor mechanism, increasing the frequency and the power of the heart-beat.

It can be especially well shown on the frog's heart that camphor can overcome a condition of standstill. As a result of stimulation of the motor mechanism, the inhibition is interrupted or the paralytic standstill resulting from narcosis of the motor centres is overcome.

If a heart which has been stopped by muscarine is exposed to camphor vapor or to NaCl solution containing minimal quantities (1–1000) of this drug, more or less frequent pulsations interrupt the standstill (*Harnack u. Witkowski*), while at the same time the persistence of the inhibition is evidenced by the well-marked diastole of the heart. Camphor, being a chemical stimulant for the motor centres, is able to overcome the inhibition, just as during a muscarine standstill each mechanical stimulation excites a contraction.

Camphor acts also as a direct antagonist to the depressant poisons. At a time when, for example, the chloralized heart is beating with extreme slowness, the application of camphor starts it beating more rapidly and the contractions become more powerful.

Even some minutes after the heart has ceased to beat camphor can start it beating again (*Böhme*). This reviving action may be most clearly shown on an isolated and perfused frog's heart poisoned by chloral, by adding camphor to the

perfusion fluid which already contains chloral. Although the heart may already be severely poisoned by chloral and continues to be subjected to its action, after camphor is added to the perfusion fluid the heart action is at once improved and the frequency and strength of the contractions are both increased. (Fig. 23.)

Camphor is thus able to revive the motor mechanism of the heart at a time when the automatic centres are threatened with extinction. As this automatic mechanism acts under ordinary conditions with maximal efficiency, the favorable action of camphor cannot be well observed on a normal heart.

The above-cited actions have been well established for the frog's heart, and it may be considered as proved that camphor will exert the same effect on the pathologically disturbed automatic centres in the hearts of the higher species. However, the experimental demonstration of this is much more difficult in mammals, for in them it is not so easy to bring about a stationary condition of disturbed heart function or to study the actions of drugs thereon.

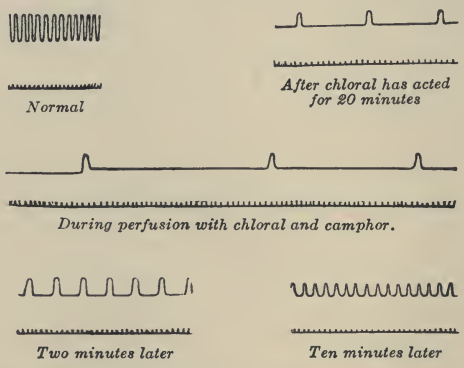

FIG. 23.—Suppression of chloral standstill by camphor in a perfused frog's heart

Camphor possesses further a distinct action in cases of a peculiar disturbance of the heart functions known as *fibrillation*. By this term is understood the violent but fully uncoördinated contractions of the whole reticulum of the cardiac muscles, a condition which may be induced in the living heart by sudden interruption of the coronary circulation, as also by acute poisoning with chloroform and other toxic substances. Fibrillation may also be readily induced in the surviving heart by direct stimulation with the induced current, such stimulation causing the surviving cat's heart to fibrillate either persistently or for some time. If, however, to the usual perfusion fluid small amounts of camphor be added and the perfusion be continued, the fibrillation ceases, and renewed stimulation with the induction current causes only momentary fibrillation (*Seligmann, Gottlieb, Klemperer,* opposed by *Winterberg*).

Suppression of the fibrillation may account for the therapeutic effect of camphor in cases where the auricle alone is affected. Fibrillation of the ventricle must quickly cause death, on account of the

interruption of the circulation resulting from it. On the other hand, in man cases are observed with very rapid and irregular pulse, presenting a clinical picture which *Cushny* and *Edmunds* have shown to resemble closely the phenomena observed in dogs when fibrillation of the auricles alone has been induced. In such cases, as soon as the auricle begins to beat regularly again, the ventricular pulse also becomes normal. The heart action during the death struggle, which is often improved by camphor, presents certain analogies with this condition.

From the above it is clear why the normal blood-pressure will not be raised by any action of camphor on the heart, although it is raised by doses which cause convulsions, this being due to stimulation of the vasomotor centres. Only when the circulation is depressed may a rise in blood-pressure result from doses not large enough to cause convulsions. The rôle played here by an improvement of the vessel innervation will be discussed later. *There is no doubt that when camphor is used to revive the circulation in dying patients, in whom the automatic centres in the heart are failing, it may exert a direct favorable action on the heart.**

Musk was formerly much used for the same indications as camphor, but to-day it is used but seldom and is no longer officinal. There are no experimental investigations which would justify its use clinically.

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ETHER.—The subcutaneous injection of ether is often employed as a cardiac analeptic (restorative), although it has not been possible to demonstrate that ether possesses a direct stimulating effect on the heart's activity. Although in conditions of collapse temporary improvement of the circulation may follow the subcutaneous injection of ether, this is, in part at least, to be attributed to the sensory stimulation caused by the powerful and, in conscious patients, very painful

* [Recently *Heard* (Am. J. of Med. Sci., 1931, vol. 135, p. 238) in a carefully conducted clinical investigation has failed to note any favorable effects on the circulation following the administration of camphor.—TR.]

irritation of the tissues which the injection causes. Its reflex effects on the respiration and circulation must, therefore, be considered as similar to those arising from other sensory stimuli. They may, in combination with the vasomotor effect of ether, contribute to the improvement of the blood-pressure and thus to a better flow of blood through the heart.

In ether narcosis the frequency of the pulse is regularly increased, in adults often to above 100, in children even more so. In experiments on animals also, the pulse frequency is regularly increased by the inhalation of not too concentrated ether vapor (*Elfstrand*), an effect quite contrary to that caused by chloroform. This, however, is not to be attributed to a direct effect on the heart, for this acceleration does not occur if the heart be isolated from the central nervous system (*Bock*). It is, therefore, of central origin, as the result of either direct or reflex actions on the centres of the extracardial nerves. This acceleration of the pulse must aid in producing the rise in blood-pressure observed at the commencement of narcosis. The action of ether on the heart may, therefore, be interpreted only as an indirect one, for up to the present time there exists no proof that it possesses a direct favorable action.

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Alcohol.—It is a still much-discussed question whether alcohol exerts a direct stimulating action on the heart. Even the behavior of the pulse has been differently determined and interpreted by different observers. As a rule, in man alcohol accelerates the pulse (*John*), but in carefully conducted experiments this has at times not been the case (*Zimmerberg, Wendelstadt*). There is no doubt that the acceleration of the pulse, when it does occur, is, at least in part, due to secondary effects of the action of alcohol on the mind, as well as to reflexes caused by its smell and taste or by its local action on the gastric mucous membrane. Recently *Dixon* observed that acceleration of the pulse did not occur after absorption of alcohol from the stomach if it were introduced highly diluted, and that, when 20 per cent. alcohol was held in the mouth for only a short time and then spit out, this acceleration passed off more quickly than when the alcohol was swallowed. In experiments on animals, secondary effects resulting from actions on the central nervous system are apparent even after intravenous injection. For these reasons, only experiments on the isolated organ are suitable for the determination of the extent to which a direct stimulant action on the motor mechanism of the heart is responsible for the acceleration of the pulse. The same holds good for the effects on the strength of the contractions.

Experiments on the isolated heart indicate that, beginning with a concentration of about 1 per cent., alcohol exerts a distinctly harmful influence on the cardiac function (*Loeb*). According to many authors who have subjected the isolated frog (*Dreser, Dieballa*) or mammalian heart (*Bock, Tunnicliffe* and *Rosenheim, Kochmann*) to the influence of even weaker solutions, only a depressant action is exerted, and all favorable action is denied. On the other hand, *Loeb,* using even smaller amounts of alcohol, observed a distinct although slight stimulant action on the surviving cat's heart perfused according to *Langendorff*. This favorable effect was obtained by the use of from 0.13–0.3 per cent. alcohol, and was especially marked in such hearts as were previously beating poorly. A favorable influence was also obtained as an after effect of stronger concentrations after the alcohol-containing blood had been washed out. *Wood* and *Hoyt* produced an unmistakable increase of the pulse volume of the frog's heart by adding 0.25–0.5 per cent. alcohol, and *Dold* obtained similar results. Nevertheless, the differences observed in the mammalian experiments were only slight ones and the results were by no means constant. This seems to indicate that the normal heart working under favorable conditions is but slightly influenced by small amounts of alcohol (just as we saw similar conditions obtaining for the action of camphor), and that only the feeble contractions observed during depressed cardiac activity are favorably influenced by suitable doses of alcohol. This is evident from *Dixon's* experiments. In these experiments, conducted on mammalian hearts perfused with Ringer's solution, with or without the addition of dextrose, the strength of the contractions was usually increased when the fluid contained 0.05–0.3 per cent. of alcohol. This positive effect was, however, much more pronounced in hearts which had previously been kept beating for hours without any addition of organic nutrient material to the perfusion fluid, while this effect was either much slighter or was entirely lacking in hearts which were beating strongly and which had been kept well nourished through the addition of glucose to the perfusion fluid. Stronger concentrations of alcohol strengthened the heart's action only temporarily, and quickly produced harmful results.

Some grounds for the belief that alcohol serves the heart as a nutrient material are found in the fact that the alcohol produces a much more pronounced stimulation in badly nourished hearts than in hearts which had been kept beating in a nutrient solution containing glucose but no alcohol. This drug easily passes into all tissues, and the experiments of *Dixon* make it probable that it may be used as a source of energy. In fact, a part of the alcohol added to the perfusion fluid is consumed (*Hamill*). Moreover, according to *Dixon,* glucose improves the action of the heart quite similarly to alcohol, and is also consumed when perfused through the active mammalian heart (*Johannes Müller, Locke* and *Rosenheim*).

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Epinephrin is a typical stimulant to the heart's activity.

The stimulation of the accelerator nerve-endings manifests itself especially in the surviving mammalian heart by acceleration of the heart rate and by a striking increase in the strength of the contractions. This effect, in contradistinction to that of camphor, also occurs on hearts which are beating well and are well nourished.

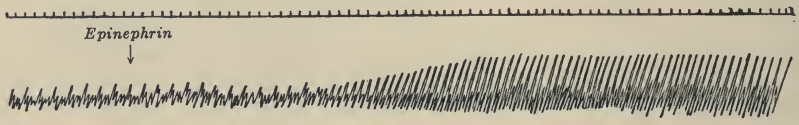

Fig. 24.—Effect of epinephrin on the isolated cat's heart.

Through its specific power of stimulating the vasomotor nerve-endings in the vessel walls, epinephrin, when injected intravenously, causes a general vasoconstriction and an enormous rise in blood-pressure. Such an increased resistance in the vessels lays upon the heart a great burden while it is emptying itself. Because of this preponderance of the action upon the vessels, it may happen that the heart breaks down as a result of the rise in blood-pressure, but, when epinephrin is injected into a depressed circulation, the blood-pressure need not rise above the normal, and then the increased power of the heart's contractions is clearly apparent.

That this is not the result simply of the indirect effect of improved blood flow in the heart, but that it is due to a direct action on the heart, is shown by experiments in which the heart has first been brought to a standstill by chloral hydrate, chloroform, or potassium salts, or else has been so depressed that it is beating very feebly and infrequently. If then epinephrin be injected into the veins and reaches the heart, the heart revives again and beats more frequently and more powerfully than at the start.

As the epinephrin is distributed around in the circulation by the restored activity of the heart and is thus able to act on the vessels,

the blood-pressure rises again very markedly, even if it had previously sunk to the zero point. This reviving action of epinephrin is, however, very fleeting, because this drug is very unstable when injected into the circulation. However, the favorable results may outlast its fleeting action in case the cause of the fall in pressure—for example, chloroform or potassium salts—has in the meantime been eliminated. In animal experiments, in cases of apparent death caused by chloroform, it is possible by the use of epinephrin to start the heart beating again.*

This cardiac action of epinephrin may be demonstrated in the isolated "heart-lung" circulation. With the heart under these conditions beating independently of all influences from the central nervous system, the frequency of the pulse increases simultaneously with the strengthening of the contractions. On the other hand, in the intact circulation the pulse is at first slow, for the rise in blood-pressure causes a central vagus stimulation, which overcomes the

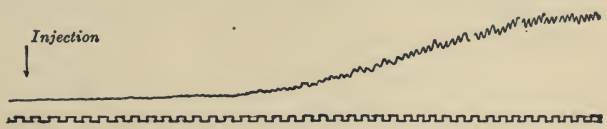

FIG. 25.—Effect of the injection of suprarenal extract 1 minute and 35 seconds after cessation of heart-beat.

tendency of the heart to contract more rapidly as a result of the direct action on the heart. Only later does the excitation of the motor mechanism of the heart gain the upper hand so that the heart may beat more rapidly.

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THE ACTION OF DIGITALIS ON THE HEART

The members of the pharmacological groups of digitalis and caffeine are also cardiac stimulants, influencing the contractions of the heart in characteristic and, for each group, different fashion.

The active principles of the digitalis leaves and a number of other glucosides occurring in very different species of plants, all produce a similar typical effect on the activity of the heart. Digitalin and digitoxin, derived from the digitalis leaves, and strophanthin, derived from strophanthus seeds, are the most important members of this group. Their typical action is characterized by an especially elective action on the heart, which is well shown during the development of the

* [Also in human beings, particularly if the action of the epinephrin be supplemented by massage of the heart.—TR.]

digitalis action on the heart of a frog. At a time when this organ, having passed through all phases of the poisoning, has been brought to a complete standstill, the frog shows no symptoms of toxic action on his nervous system, and, inasmuch as the nervous system of cold-blooded animals preserves its excitability for a considerable period after cessation of the blood flow, the frog is still able to hop around quite normally.

In the following discussion the substances belonging to the pharmacological group of digitalis will be spoken of, for the sake of brevity, as digitalis bodies, or substances, although typical members of this group occur in other plants.

Action on the Frog's Heart.—If a full dose of a digitalis body be injected into a Rana temporaria, the following phenomena may be observed on the exposed heart (*Böhm*). After some minutes the relaxation appears to be increased, and to last somewhat longer than normally. The frequency of the beats is slightly diminished, while the contraction is more energetic,—that is, the ventricle at the height of its contraction is paler than it was before administration of the drug, as it drives out its contents more completely. Then there occur occasional temporary diastolic pauses, and later the movements of the heart become strikingly irregular, owing to the fact that all portions of the ventricle are no longer equally relaxed in each diastole. As these partial diastoles of the different parts of the ventricle do not occur with any regularity, the blood is shoved hither and thither in the heart, and the peculiar picture of "heart peristalsis" develops. This phase, which is often interrupted by a series of regular heart-beats, is succeeded sooner or later by a persistent contraction of the ventricle (systolic standstill), which represents the characteristic final stage of the pharmacological action. The ventricle remains completely contracted and emptied of blood, while the auricle, distended with blood to bursting, continues to beat for some time, finally passing into a condition of stoppage in diastole. Even after the heart has passed into the phase of systolic standstill, it has by no means lost its power of beating, but the tendency of the ventricle to remain in a contracted condition prevents its relaxation. If at this stage relaxation is artificially brought about through hydrostatic pressure, this forced diastole is followed by a series of active heart-beats (*Schmiedeberg*). This standstill is, therefore, at the beginning to be considered as due to a persistent stimulation of the contracting mechanism and not as due to a paralysis. However, the cardiac muscle finally becomes unexcitable and dies in a state of contraction.

A closer analysis of the characteristic course of this poisoning is especially interesting, for these first actions on the frog's heart exhibit features of that digitalis action which is of importance in its therapeutic application. Such closer analysis is possible only on the isolated heart, for the heart acting in conjunction with the whole

circulation is influenced by secondary factors,—for example, by the changing inflow of blood from the vessels.

It, therefore, was significant of a decisive advance in our knowledge of digitalis when *Böhm,* in 1872, and, later and more completely, *Williams* investigated the actions of the digitalis bodies on the frog's heart beating in an artificial circulation. It was shown by this author that the diastolic relaxation was increased quite independently of any retardation of the rate, the ventricle relaxing to a greater extent under an unchanged diastolic pressure, while the systolic contractions pump out this greater content very completely. The pulse volume of the heart, therefore, increases, as does the pulse pressure in the artificial circulation, and thus the "heart work" accomplished by each contraction is increased, as is also the work done per minute, unless the rate of the heart-beats is too greatly diminished.

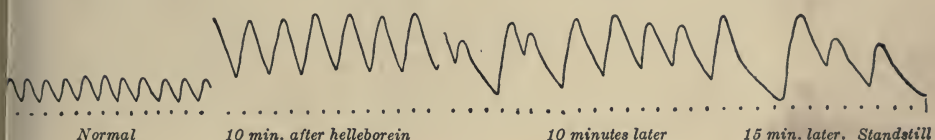

Fig. 26.—Tracing from frog's heart (*Williams*).

In this first phase the digitalis bodies produce two effects on the cardiac function by a *"systolic"* and a *"diastolic"* action. The "diastolic" action expresses itself in the retardation of the heart's action and in the increase of the relaxation. The "systolic" action has its expression in the more complete and energetic pumping out of the ventricular contents. The heart under the influence of digitalis works like a pump, the piston of which at each stroke is raised higher and pushed in again more completely. The absolute power of the heart, however, is unchanged,—that is, the piston of the pump is not more forcibly moved nor is it able to overcome any higher pressure than before. The heart does not gain in muscular power, but simply utilizes its power more efficiently.

The slowing of the frog's heart which is caused by digitalis occurs quite independently of the vagus centre and of any action on the vagus nerve-endings. While previous atropinization produces no effect, still the "diastolic" digitalis action resembles to a marked degree the vagus inhibitory action, and actually finally causes a lasting diastolic standstill of the frog heart beating in connection with the frog-heart manometer, if the digitalis bodies have been added to the nutrient fluid in quantities distinctly smaller than those which, under like conditions, cause the systolic standstill (*Werschinin*). This standstill in diastole occurring after very small doses of digitalis is the maximal expression of the "diastolic" action of digitalis, while the systolic standstill is that of the "systolic" action. In the frog under the conditions of the normal circulation, the "systolic" action always gains the upper hand when the dose is large enough to produce any effects. However, during the gradual absorption of small doses one may observe, in the intact frog or with a Williams apparatus, a contest between the two actions, during which fairly long diastolic pauses occur before the systolic stoppage takes place.

The "diastolic" digitalis action—slowing of the heart rate and increase of the relaxation—resembles an inhibitory action, and the strengthening of the contractions reminds one of a stimulating action on the accelerator nerves, but they both occur quite independently of the extracardial nerves. It is not possible at the present time to determine which of the elements in the heart are acted on by the digitalis bodies.

THE ACTION ON THE ISOLATED MAMMALIAN HEART is fundamentally similar to that on the frog's heart, except that in the mammalian heart the "diastolic" digitalis action is overshadowed by the systolic (*Hedbom*). The slowing of the pulse, which in man is well marked after medicinal doses, as also in the early stages of poisoning in the higher animals, is not caused peripherally, as is the case in the frog's heart, but is, at least in the case of most of the pure principles thus far investigated, entirely the result of stimulation of the vagus centre. It therefore does not occur after section of the vagi, or after destruction of the central nervous system, or after atropine (*Ackermann, Kochmann*).

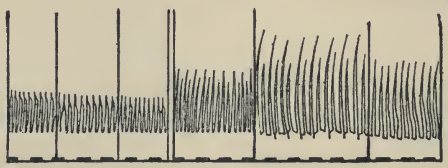

FIG. 27.—Curves obtained from a surviving cat's heart.

That "diastolic" action of digitalis which occurs independently of the vagus is only faintly indicated in the mammalian heart under the influence of this drug, although a more pronounced relaxation in diastole has been observed in the cat's heart when perfused with digitalis according to Langendorff's method. On the contrary, the pulse frequency of the mammalian heart is markedly increased when it is isolated and rendered independent of the central nervous system and subjected to the influence of digitalis. It may be that this preponderance of the accelerator action is responsible for the fact that the "diastolic" action of digitalis, which is so well developed in the frog's heart, is barely indicated in the mammal.

In the isolated mammalian heart the "systolic" digitalis action causes a more complete contraction, in which evidently both ventricles are involved (*Brawn u. Mayer*). The effect of the more complete systole on the blood-pressure and on the pulse volume of the heart can be measured by inserting into the empty ventricle a balloon which just fills its cavity and which measures the changes in its pressure and volume. Under the influence of the digitalis bodies the work done

by a single contraction of the heart can be augmented 2½ to 3 times (*Gottlieb u. Magnus*).

As the poisoning develops these early effects are followed, just as is the case with the frog's heart, by irregularity of the heart action, and finally, as the heart relaxes less and less, the heart stops in a state of maximal contraction. This systolic standstill of the mammalian heart may also at first be removed by forcible dilatation of the contracted muscle-fibres.

The fact that the heart, beating in the intact circulation, finally stops in diastole instead of in systole is not due to a qualitative difference in the end stages of the toxic action in cold- and warm-blooded animals, but to the greater susceptibility of the mammalian heart to an interruption of its coronary circulation, the harmful effect of even moderate diminution of the diastolic relaxation so interfering with the blood supply of the heart muscles that, unless the heart be artificially perfused, the further development of the augmentation of the systolic contraction is interrupted.

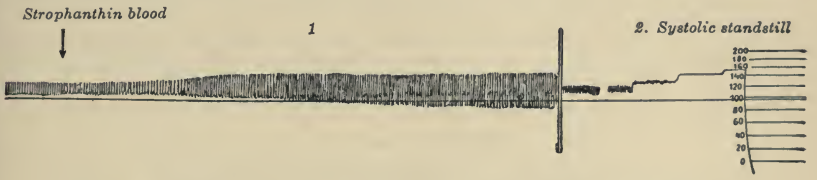

FIG. 28.—1. Increase in the variations of the intraventricular pressure after strophanthin. 2. Their progressive diminution until finally the heart stops in systole.

Another fundamental action of digitalis, that of regulating a previously irregular cardiac action, is well brought out on the isolated mammalian heart. Even after small dosage this action is clearly developed and is therapeutically of great significance, but thus far this action is not susceptible of a closer analysis (see p. 266).

It may readily be understood that the improvement of the cardiac function by digitalis will be materially dependent on the character of contractions at the time when the drug is used. If before its administration the systolic contraction is already a nearly optimal one, the augmentation of the heart's performance will not be so great as it would be in case the contractions were feeble. This action may, therefore, be better demonstrated on a Langendorff's heart preparation which is relatively poorly supplied with blood, and which is beating relatively weakly, than on a fully normal organ, which is normally contracting nearly to its full extent in the circulation of a healthy animal (*Magnus u. Sowton*). *Bock,* in his experiments with the "heart-lung" circulation, found that the rise in blood-pressure resulting from an increase of the pulse volume of the heart was especially striking in hearts which had been beating inefficiently.

An augmentation of the pulse volume of the heart beating in the intact circulation must, under otherwise equal conditions, cause an increase of the aortic blood-pressure. In accord with this the mean

pressure in the Williams frog-heart apparatus is increased by the digitalis bodies (see curve, Fig. 26, p. 263).

On the other hand, the pressure in the pulmonary arteries is not increased, or at least is much less increased than the pressure in the aorta. This difference is not due to a different action on the two ventricles, but to the fact that the pulmonary vessels are more readily distended and may be more easily filled without increasing the resistance in them (*Wood, Openchowski, Mellin, Plumier*).

The volume changes of the ventricle may be measured in the living animal by means of the plethysmograph or similar instruments (*Cushny*), a diminution of the heart volume in systole justifying the conclusion that its contents are more completely expelled. The total amount of work done by the heart beating in the intact circulation depends, however, not alone on the pulse volume of the single heart-beats but on the pulse frequency. In the therapeutically important stage of their action, the stimulation of the vagus centre by the digitalis bodies may so diminish the number of heart-beats that the minute volume of blood pumped out by the heart is, as a result of this slowing, increased only moderately, or may in fact be actually diminished.

After toxic doses of digitalis a sudden change in the rate of the pulse, from retardation to acceleration, may occur. This is due to a peripheral vagus depression or, more correctly expressed, to an over-excitability of the heart that renders it less susceptible to vagus inhibition. With large enough doses there finally develops irregularity of the heart action, and usually the heart stops very suddenly in diastole or in systole (see above).

[To-day no discussion of the action of digitalis on the heart is complete unless it includes at least a brief consideration of its effects on the functions of conductivity and irritability or excitability (see p. 244). Largely through the admirable work of *Mackenzie,* augmented by the observations of *Cushny, Lewis,* and others, it appears to be established that in laboratory animals and in man under clinical conditions, digitalis and its congeners produce a distinct retarding effect on the conductivity of the Bundle of His, varying from a slight retardation to a complete blocking. As especially pointed out and emphasized by *Mackenzie,* this complete or partial blocking effect of digitalis may be of decisive importance for the therapeutic effect produced, resulting at times to the advantage and at others to the disadvantage of the patient. Clinical observations, combined with subsequent post-mortem examination, have demonstrated that certain pathological changes in this Bundle of His favor the development of this blocking effect.

In this connection it appears well to emphasize the clinical importance of the action of digitalis in exciting or rendering more irritable the motor ganglia or centres in the heart, for it has been established

clinically that under the influence of digitalis the tendency to premature contractions or extra systoles may be decidedly aggravated. It should, however, be stated at the same time that, by its other actions on the whole circulatory system, the administration of digitalis may bring about a generally improved circulation, although increasing the tendency to extra systoles, or at times causing them to diminish in frequency or disappear at least for an indefinite period.—Tr.]

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Caffeine.—To the discussion of the pharmacology of the digitalis group succeeds that of caffeine, which is often considered by clinicians to resemble digitalis. Its chief action on the circulation is, however, exerted upon the vasomotor centres, but it is necessary to make clear how the heart behaves under these conditions. If caffeine raises the blood-pressure, there necessarily results an improvement of the cardiac action, for, on account of the narrowing of the vessels, more blood flows back into the heart.

In an isolated frog's heart, rendered independent of indirect influence through changes in the blood-vessels, it is not possible to demonstrate that there is any increase in the work done against the normal resistance, and large doses quickly exert a harmful effect on the heart, while even after small doses the pulse volume of the frog's heart is not distinctly increased (*Maki*). On the other hand, even after small doses there is an augmentation of the "absolute power" of the heart,—that is, it is able to empty itself against a greater resistance than before (*Dreser*[1]). We have here an action on the cardiac muscle analogous to the action of caffeine on voluntary muscles, the absolute power of which is also increased by caffeine (*Dreser*[2]).

Difference in Cardiac Action of Caffeine and of Digitalis.—In accordance with the above, the action of caffeine on the frog's heart is quite different from that of the digitalis bodies. In contradistinction to those drugs, caffeine has no favorable "diastolic" action. On

the contrary, from the start it lessens the extent of relaxation and thus, especially in the mammalian heart, diminishes its pulse volume. This results from the fact that caffeine increases the tendency of the cardiac muscle to remain contracted, just as it does with voluntary muscles, and at the same time it hinders the relaxation of the heart in diastole. While one may compare the heart under the influence of digitalis with a pump the piston of which makes greater excursions but is unable to overcome any greater maximal pressure, under the influence of caffeine the volume of blood forced out by single contractions is at no time increased, but the heart can overcome a greater maximal blood-pressure. A favorable action on the heart could, therefore, result, especially when there is an abnormally high resistance in the vessels. The observations of *Bock* on the "heart-lung" circulation of the rabbit are in accord with these conclusions.

Although, on the other hand, *Hedbom* observed that in the mammalian heart, perfused according to *Langendorff*, caffeine caused both an increase in the frequency and a distinct increase in the amplitude of the heart-beat, this may be explained by its specific power to dilate the coronary vessels. The improved blood supply thus obtained increases the strength of the contractions in the artificially perfused heart to such a degree that any diminution in the diastolic relaxation is compensated for.

Caffeine accelerates the action of the isolated mammalian heart by a direct action in the heart. As this occurs after atropine and as the vagus nerve-ends remain excitable (*Wagner*) this pulse acceleration cannot be the result of a depression of the inhibitory mechanism, but is due to a stimulation of the cardiac accelerator mechanism.*

The acceleration of the pulse after caffeine is well developed in the first stages only if the heart is beating independently of the control of the central nervous system. On the other hand, in the intact animal caffeine excites the vagus centre just as it does other nervous centres. With small doses this effect is the predominant one, so that usually at the start the pulse is retarded if the vagi are intact. In man also (*Riegel, Kunkel*) the pulse may be slowed by therapeutic doses of caffeine (0.2–0.5 gm.).† Only after larger doses does the acceleration of the pulse occur, this being a result of a direct action on the heart.

After toxic doses, and also temporarily after the intravenous injection of the small doses, in experiments on animals, the heart action becomes feeble and arhythmic, and finally fibrillation of the heart develops and the heart stops in diastole.

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* [Like digitalis caffeine also by its action on the intracardiac motor mechanism may cause or aggravate a tendency to premature contractions (extra systoles).—Tr.]

† [In man the rule is that caffeine accelerates the pulse.—Tr.]

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Other Factors Affecting the Heart Action.—From experiments on the surviving mammalian heart, it is known that its excitability and capacity for work depend to a great degree on the temperature and on special chemical conditions,—that is, on the correct composition of the perfusing fluid. A considerable rapidity in the flow of the nutrient solution is also necessary for the maintenance of the normal chemical processes in the mammalian heart, for it would appear that the demand for oxygen made by the actively beating heart necessitates this rapid flow. On the other hand, a heart may beat for hours in a hæmoglobin-free fluid or in blood rich in carbon monoxide (*Strecker*), the small quantities of oxygen absorbed by the salt solution being sufficient to maintain this function. However, the power of the contractions of the mammalian heart and its capacity for work are dependent in a high degree upon the supply of oxygen, just as is the case with every muscle (*Rohde*).

A rapid flow through the vessels of the heart is also necessary to remove or to neutralize those metabolic products, resulting from the cardiac activity, which exert a depressant action on the heart. Such a substance is, for example, carbon dioxide, the accumulation of which in the heart inhibits its activity.

For the maintenance of the chemical equilibrium in the heart, we need a nutrient medium adjusted properly to this equilibrium. Each smallest alteration in the proportions of the chemical constituents of the nutrient solution—for example, the loss or removal of any of them, especially the loss or diminution of the calcium salts—causes severe disturbances, just as in all other susceptible organs. Especially in the heart these disturbances are quickly and clearly manifested by changes in its automatic activity.

Physiological sodium chloride solution alone is not capable of maintaining the function of the heart for any considerable period, the heart becoming exhausted and being harmfully effected by it, so that its excitability and functional powers gradually fail (*Martius*). The heart function is maintained far better by a solution containing all the salts normally present in the blood,—*e.g.*, those of the blood ash (*Merunowitsch*). As solutions which besides NaCl and a calcium salt also contain Na_2CO_3 or NaOH act more favorably, the significance of the alkaline salts of the blood may be sought also in their power of neutralizing acid metabolic products (*Göthlin*). According to all more recent investigations, calcium appears especially important. *Ringer* was the first to show that, in addition to common salt, CaCl and KCl must be present in the nutrient solution in order to obtain the

best possible performance by the heart. An improvement in the function of cold- and warm-blooded hearts results from the addition of calcium to a solution containing enough NaCl to maintain the proper osmotic pressure. Such addition causes increased and more energetic contractions, but gradually the relaxation becomes incomplete and the heart-beats thus become less efficient (*Langendorff*). Potassium, on the other hand, if added by itself to the NaCl solution, favors relaxation and ultimately causes a diastolic standstill. Calcium and potassium are thus seen to work antagonistically to each other and, when both are present, to compensate each other. In the proportions used in Ringer's solution the calcium preponderates. Under the conditions obtaining in the blood in which both of these ions are present, we are, therefore, dealing with a compensated calcium action (*Ringer, Gross*).

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PHARMACOLOGICAL ACTION ON THE VESSELS

Like the heart, the vessels have a double innervation through the vasoconstrictors and vasodilators, their interplay maintaining the compensatory regulations in the circulation by which the blood supply of the vital organs is preserved (see page 231 ff.). With the assistance of the vasomotor centres, the regulative constriction of other vascular systems is brought about when any vascular system is dilated, and in the same fashion vasoconstriction of one system is compensated for by vasodilatation in others, so that the blood supply of the organs can vary within large limits, according to their changing needs, without any alteration in the general blood-pressure. In numerous pharmacological actions a similar mechanism is called into play, so that under their influence only the distribution of the blood is altered, the pressure in the aorta remaining constant.

Probably the vasoconstrictors as well as the vasodilators control these compensations in the vascular system. Their coöperation would appear to be secured by means of a reciprocal intracentral inhibition, so that, for example, decreased tonus of the vasoconstrictor centres automatically results in a stimulation of the vasodilator centres. The two mechanisms thus normally never act in opposition, but always together.

As a result of this double innervation any change in vessel calibre —for example, relaxation in a particular vascular system—may occur

in two ways,—either by depression of the vasoconstrictors or by stimulation of the vasodilators. Both of these effects may be due to an action on the centres or on the peripheral mechanism.

There are also in the vessel walls peripheral vasomotor nerve-ganglia, pharmacological action on which cannot be differentiated from that on the terminal mechanisms. The existence of these peripheral vasomotor nerve-ganglia is proved by the fact that, even after separation from the central nervous system,—for example, after section of the vasomotor nerves,—certain vascular systems do not remain maximally dilated but gradually regain their power to react. The significance of this peripheral vascular tonus is best demonstrated in the experiments of *Ewald* and *Goltz*, in which, after destruction of the dorsal and sacral cord and section of the sciatic of the dog, there developed in the lower extremities a vascular tonus independent of all central influence. The intestinal vessels also, after section of the splanchnics, gradually regained their tonus with the assistance of peripheral mechanisms, and the blood-pressure was re-established.

Finally, alterations of vessel calibre depend, in the last instance, on the muscles in the arterial walls. An example of a probably direct action on these muscles may be seen in the vasoconstriction produced by barium salts. However, it is hardly possible to differentiate with certainty between a pharmacological action on nerve-endings in the vessel wall and that on their muscles.

All these changes in the calibre of the vessels may affect only one vascular system or many at one time. In such case, the central action on the vessel innervation and the peripheral changes in the vessel wall produced by one and the same drug may cause similar or opposite effects, so that, for example, vasodilatation in the kidney, due to a peripheral action, may occur at the same time with vasoconstriction in other situations, this latter being the result of a central action. It is thus comprehensible that the distribution of the blood may be affected by drugs in the most manifold fashion.

That under these conditions the aortic pressure remains unchanged is due to the already discussed compensating mechanism of the circulation, the behavior of the vessels of the intestine, the liver, and the spleen being of decisive importance for this power of accommodation. On account of its great capacity, the portal system is able to furnish enough blood for the filling of the other vascular systems, or, on the other hand, as a result of its great distensibility, it is able to accommodate blood forced out from other parts of the body, thus compensating for vasoconstriction elsewhere.

Only by the investigation in detail of the different vascular systems—for example, by means of plethysmography—is it possible to recognize these variations in the distribution of the blood, as long as in their early stages their effect on the aortic pressure is compensated

for by the compensatory behavior of the different vascular systems. Only very pronounced vasomotor effects cause changes in the aortic pressure.

By stimulation of the splanchnic *Mall* was able to transfer 27 per cent. of the total blood contents of a dog from the portal circulation into other systems, the splanchnic stimulation causing constriction not only of the arteries but also of the veins in the portal system (*Schmid*).

The SPLANCHNIC acts as the chief regulator of this compensating function. For this reason the blood-pressure in the aorta remains normal, even if, for example, the vessels of the skin be ever so extremely dilated by antipyrine. However, the total cross-section of the arterial tree may be maintained constant only as long as the portal system remains under the control of its vasomotor innervation, for any marked dilatation of the hepatic and intestinal vessels cannot be compensated for, and, therefore, if vasomotor depressants, such as certain bacterial toxins, act on the centres controlling the visceral vessels, this compensation does not occur and the aortic pressure sinks.

Constriction of the visceral vessels mechanically and reflexly forces the blood into other vascular systems. If, for example, the vessels of the skin and muscles are dilated while simultaneously the splanchnic vessels are constricted, it may be a question whether this be due to a direct action in dilated systems or to expulsion of the blood from the visceral vessels into those of the skin and muscles. This point must be especially remembered in considering the early stages of the action of alcohol and ether, as also in connection with the dilatation of the cutaneous vessels in atropine poisoning.

In the different species the relative importance quantitatively of the different vascular systems can vary greatly. In particular, it is difficult to compare the cutaneous vessels of man with those of the animals used in our experiments, for in man the skin, as an important organ for the loss of heat, plays a quite different rôle from that played by the hide of these animals, and accordingly in man the cutaneous vessels are much more numerous and more subject to nervous influences. Moreover, the different relative size of the extremities and the trunk in man and in the small laboratory animals is a further factor to be considered. On the other hand, the length of the alimentary canal has an effect on the influence exerted by the splanchnic vessls on the distribution of the blood. For this reason, after section of the splanchnic, the blood-pressure does not fall as much in the dog as in the rabbit.

As a result of the above-described compensatory mechanism in the circulation, we may expect only an alteration in the distribution of the blood, without change in the general blood-pressure, to result from the moderate vasomotor effects of drugs. Only if a pharmacological action overcomes this regulation will the circulatory condition in the whole body be affected and the carotid pressure be changed.

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CENTRALLY ACTING VASOCONSTRICTING DRUGS

STRYCHNINE.—The excitability of the vasoconstrictor centres is augmented by strychnine in the same way in which the spinal reflexes controlling motor functions are rendered over-excitable by this drug. With the maximal development of the strychnine action, therefore, a tetanus of the muscles of the vessel walls occurs simultaneously with the outbreak of the tetanus of the striped muscles, and thus the aortic pressure is tremendously raised. This vascular cramp is, however, independent of the tonic contractions of the voluntary muscles for it occurs in the curarized animal (see Fig. 29). The vagus centre is also stimulated simultaneously with the vasomotor centres (*S. Mayer*).

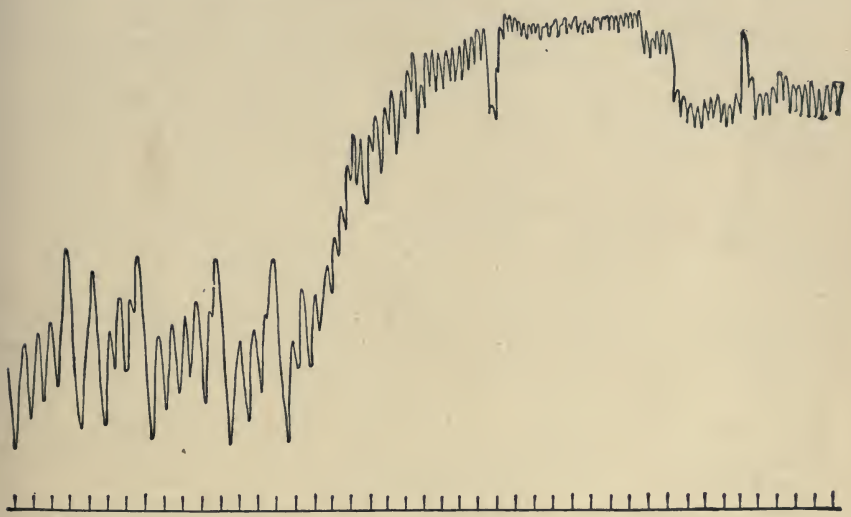

FIG. 29.—The effect of strychnine on the blood-pressure of a curarized cat.

After division of the cord in the neck, strychnine raises the blood-pressure to a much slighter extent, but some rise does occur, especially in young animals, so that, after isolating the vascular system from the main centres in the medulla, strychnine may be used to demonstrate the existence of accessory vasomotor centres in the spinal cord (*Schlesinger*). On the heart, strychnine exerts a depressing influence only in doses which are much larger than those causing convulsions (*Igersheimer*).

All of the vascular systems are by no means equally affected by strychnine. On the contrary, practically only the vessels in the portal system are constricted, as may be shown by the simple inspection of the exposed intestines. Plethysmographically, diminution in their volume—for example, in the kidney—may be demonstrated while the peripheral vessels may be shown to be dilated (*Wertheimer et Delezenne*).

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Caffeine's action on the vasomotor centres is analogous to that of strychnine, just as large doses of caffeine cause convulsions. However, the stimulation of the vasomotor centres by caffeine does not result in as marked a rise in pressure, because the action of the caffeine on these centres is complicated by the influence exerted at the same time on the frequency of the pulse and on the pulse volume of the heart. In animals it may be demonstrated that especially medium-sized doses cause an increase in blood-pressure, while still larger doses produce no change in the blood-pressure. Very large doses, as well as very rapid direct injection of the drug into the veins, cause a fall in pressure, resulting from the depression of the functional power of the heart, which is undoubtedly caused by the strong concentration of caffeine acting directly on the heart (see p. 268).

Besides acting on the vasomotor centres, caffeine acts also on the vessels in the periphery. This action on the vessel walls is, however, the opposite of its central action, for by its peripheral action it dilates the vessels of the heart, kidney, and brain. The two dimethylxanthines, theobromine and theophylline, also possess this peripheral vasodilator action (see p. 330), while their action on the vasoconstrictor centres is much less pronounced, although they, in their chemical nature and pharmacological action, closely resemble caffeine.

Camphor, picrotoxin, and other medullary convulsants also stimulate the vasoconstrictor centres. Doses large enough to cause convulsions raise the blood-pressure, for the constriction of the visceral vessels overcomes the regulatory mechanism which ordinarily prevents any alteration of the general pressure (*Wiedemann*). In such case the blood distribution is similar to that resulting from the action of strychnine and caffeine. It is probable that camphor can exert a favorable action on depressed vasomotor centres, for in experiments on chloralized animals these centres, which had become insusceptible to stimulation by asphyxia or by sensory reflexes, again became excitable (*Alexander-Lewin*). Simultaneously with the vasoconstriction in the interior of the body, the cutaneous vessels are dilated.

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Alcohol affects the calibre of the vessels in different organs in a very manifold fashion. The cutaneous vessels are dilated even by small doses, while in the first phases of its action the visceral vessels

appear to be constricted. It is probable that the dilatation of the cutaneous vessels is only partly the result of the constriction of the visceral vessels. Like many other pharmacologically closely related substances, alcohol possesses the power of slightly lessening the central vasoconstrictor tonus for the cutaneous vessels, but the accompanying constriction of the visceral vessels, which is produced by small doses of alcohol, is in part due to a peripheral action, and, according to *Dixon,* also in part a result of central action. In consequence of these opposite effects on the different vascular systems, a change in the blood distribution but no important change in the blood-pressure may be expected to result from small doses of alcohol; but after intravenous injection of appropriate doses the vasoconstriction in the splanchnic system may be pronounced enough to raise the pressure in the carotid (*Dixon, Haskovec, Kochmann*), while with still larger doses alcohol dilates not only the cutaneous vessels but also all the others, and, as the splanchnic vessels are affected with the others, the blood-pressure falls.

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Ether.—According to *Derouaux,* ether similarly affects the distribution of the blood. In the dog a slight rise in blood-pressure is observed after subcutaneous injection, but this is much more marked after the intravenous injection of a properly chosen dose. As shown by the plethysmographic curves, the visceral vessels are constricted and those in the periphery dilated during the period of increased blood-pressure. The early rise in blood-pressure during narcosis and the improvement of the heart action following hypodermic injections of ether (see p. 257) are to be explained as reflex actions caused by the irritation produced by the ether in the mucous membranes or at the point of injection. [This conclusion, that this is the sole cause of the rise in blood-pressure observed in narcosis, appears to the translator not justified either by the clinical or the experimental evidence.]

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The behavior of the cutaneous and visceral vessels during the early stages of the action of alcohol and ether is a good example of the quantitative differences in the reaction of the different vasomotor centres to identical pharmacological influences. The cutaneous vessels react readily to the dilating action of the narcotics, but the splanchnic vessels only after much larger doses. This especial susceptibility of the cutaneous vessels to the dilating action of centrally depressing drugs is best developed in the vessels of the face. The

other cutaneous vessels are dilated only after larger dosage, while the vessels in other parts of the body are the last to be affected. Of such causation is the flushing of the face during ether narcosis or at the start of chloroform narcosis and that caused by the drinking of wines with strong bouquet, as well as by morphine in certain individuals. It is most strongly expressed during the action of amyl nitrite.

The antipyretics and atropine cause redness of the skin in an especially elective fashion, no other vessels being dilated even by quite large doses. One might be tempted to attribute this action of the antipyretics to depression of the vasoconstrictor centres, and in the case of atropine, with its power of acting as a general central stimulant, to stimulation of the vasodilator centres. It is not possible, however, to decide positively between these two possible seats of action. Perhaps both mechanisms are simultaneously influenced by these drugs but in different directions, just as physiologically these centres ordinarily compensate each other as a result of their antagonistic actions.

CENTRALLY ACTING VASODILATING DRUGS

Narcotics.—In large doses narcotics of the alcohol group, especially chloroform or chloral hydrate, and also numerous alkaloids,—*e.g.*, morphine in toxic doses,—cause a gradual diminution in the excitability and finally a general paralysis of the vasomotor centres, the pulse becoming soft and the blood-pressure gradually falling. The same is true of numerous other central depressants and especially of bacterial toxins,—for example, diphtheria toxin.

Amyl nitrite is the most powerful of these vasodilating drugs, the inhalation of the fumes of 2–5 drops causing almost instantaneous flushing and a feeling of warmth of the face, pulsation of the carotids, and acceleration of the heart-beats. At the same time the head swims and a feeling of slight drunkenness develops. The brilliant redness of the skin extends from the face over the throat and chest, but rarely extends below the waist. After a few minutes the effects of small doses pass off.

The temperature of the profusely reddened skin is raised, thermoelectric measurements indicating a rise in temperature of the skin of as much as 3° C. (*Arntz, Lahnstein*).

In man it has been demonstrated that the vasodilatation produced by small doses is confined to the skin of the head and trunk and to the vessels of the brain, while probably the coronary vessels are also affected even by small doses. The dilatation may be particularly well demonstrated in the rabbit's ear, especially in tracheotomized subjects, as by this means it is possible to exclude the disturbing reflexes due to the action of the irritating vapor on the nasal mucous membrane. The participation of the cerebral vessels may be proved by inspection of the pia mater of trepanned animals, or by measuring

the blood flowing out of the cerebral veins (*Gärtner u. Wagner, Schüller, Schramm, Hürthle*). *Mosso* was able to observe an increase in the volume of the brain in a case with a cranial defect. Plethysmographic curves were taken at the same time from the forearm and foot, and it was found that vasodilatation in the forearm occurred somewhat later than the increase of blood flow to the brain, while during the action of the drug the volume of the foot was constantly diminished below the normal.

The radial pulse is larger and softer during the action of amyl nitrite, its rate rising, after a few inhalations, approximately from 75 to 98 in the minute. Animal experiments similarly show a fall in blood-pressure and acceleration of the pulse.

That the vasodilatation is due primarily to an action on the centres was proved by the experiments of *Filehne,* who caused rabbits to inhale amyl nitrite, the blood circulation in the brain and medulla being part of the time maintained and part of the time interrupted by clamping the internal carotids and the subclavian arteries. The vasodilatation in the rabbit's ear did not occur when the circulation of the brain was interrupted, although the blood flowing through these vessels contained the drug. In other experiments in which the circulation through the centres was intact and in which the drug reached them, the vessels of the ear dilated even when these vessels were supplied with blood containing none of the drug.

In large quantities, however (quite independently of its action on the centres), amyl nitrite depresses the tone of the vessels by a peripheral action. This peripheral vasodilating action of amyl nitrite is perhaps of considerable therapeutic significance. That such peripheral action occurs is proved by the fact that the blood-pressure falls during inhalation of the drug, even when, by previous section of the cervical cord or by ligation of all arteries supplying the brain, the principal vasomotor centres have been eliminated (*Lauder-Brunton,*[1] *S. Mayer u. Friedrich*).

[1] That in this case the action takes place in the vessel wall and not in the subsidiary centres in the cord is indicated by the results of perfusion of isolated organs, as also by the fact that injection of a nitrite into the carotid causes at first dilatation of the vessels of the brain alone (*Biedl u. Reiner*).

In toxic doses the blood-pressure is markedly lowered, and the rapid pulse becomes weak, but this is not due to an impairment of the heart's function, for the isolated heart is depressed only by still larger doses (*Bock et al.*). The fall in pressure and the enfeeblement of the pulse after toxic doses are, therefore, only the results of a general vasoparesis.

As after section of the cervical vagi the increased frequency of the heart action does not occur, it is clear that the acceleration of the pulse is also an indirect effect due to the depression of the cardio-inhibitory centre, this resulting automatically from the fall in blood-pressure, for in *Filehne's* experiments the acceleration of the pulse disappeared if the blood-pressure was restored to the normal by temporary clamping of the abdominal aorta.

When the cardiac nerves are intact, it is a general rule that the frequency of the pulse increases with the fall in the general blood-pressure. The importance of this regulatory mechanism may be especially well demonstrated with amyl nitrite if its effects on the blood-pressure in the dog and rabbit be compared. In the dog the blood-pressure is only moderately lowered by this drug, because, simultaneously with the vasodilatation, the pulse becomes much more rapid. In the rabbit, on the other hand, as its vagus tone from the beginning is weak, the pulse-rate is much less increased, and the blood-pressure, therefore, markedly falls (*Lauder-Brunton*[2]). In man, even after small doses the pulse is markedly accelerated.

Toxic effects result from the continued inhalation of amyl nitrite, while nausea and vomiting are sometimes observed even after small doses. Such grave symptoms as fainting and collapse after large doses are due to the general vasoparesis. Grave poisoning has been seldom observed in man, as the effects resulting from the inhalation pass off very rapidly, and as amyl nitrite is only slowly absorbed from the stomach, so that 3 gm., in fact even 12 gm., taken by mouth have not caused fatal poisoning (*Rösen*). In animal experiments long-continued administration of large amounts of amyl nitrite causes convulsions, as well as a transformation of hæmoglobinæ into methæmoglobin, an action which is characteristic of all nitrites (*Gamgee, Giacosa*).

This action on the vessels is a nitrite action, although other amyl ethers dilate the vessels,—for example, amyl chloride, which, according to *Hay,* may be used for the same indications as amyl nitrite. Ethyl alcohol and other narcotics of this group also possess a similar action. However, the vasodilatation resulting from very small doses, which is characteristic of amyl nitrite, as well as the formation of methæmoglobin after large doses, is dependent on the nitrite radical, for the salts of nitrous acids, such as sodium nitrite, produce the same pronounced effect on the vascular systems.

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PERIPHERALLY ACTING VASOCONSTRICTORS

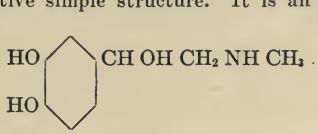
Pharmacological action in the vessel walls may be due to an action on the nervous elements in the vessel wall or to an action on the contractile substance. However, we possess no methods which enable us

to differentiate between these two possible seats of action in peripheral vasoconstriction or dilatation.

Epinephrin, cocaine, and the digitalis bodies stimulate the tone of all vessel walls [pulmonary and coronary vessels?—Tr.] In 1895 *Oliver* and *Schaefer*, and at the same time *Czybulski* and *Szymonovicz*, discovered that intravenous injections of extracts of the suprarenal glands caused an enormous rise in the blood-pressure.

Epinephrin.—Immediately after this *Moore* demonstrated that the active substance was present only in the medullary portion of the glands, and that it was identical with a chromogenic substance, described by *Vulpian* as early as 1856, possessing striking color reactions,—green coloration with iron chloride on the addition of alkalies, or with iodine or chlorine water a pink-carmine color. These reactions suggested brenzcatechin, and *v. Fürth* succeeded in preparing from this chromogen, a substance which in its behavior agreed with brenzcatechin. The crystallized active substance was first prepared in 1901 by *Takamine* and named by him adrenaline. Other authors have given it the names of suprarenin, paranephrin, epinephrin, epirenan, etc. [As the council of Pharmacy and Chemistry of the A.M.A. has recommended "epinephrin" as the preferable name, this name will be used throughout this translation.] This substance, having the empiric formula $C_9H_{13}NO_3$, is a base which is soluble in water and readily decomposes in alkaline solution, the solutions, like those of brenzcatechin, turning first red and then brown when exposed to the action of light.

The constitution of epinephrin has been determined as that of a brenzcatechin derivative of relative simple structure. It is an aminoalcohol $(OH)_2C_6H_3$ CH OH CH_2 NH CH_3



which may be prepared by reduction of methylaminoacetobrenzcatechin.

Stoltz and *Dakin* have succeeded in synthetically preparing epinephrin and a series of related brenzcatechin derivatives, which, according to *Loewi* and *Hans Meyer*, possess an action fully analogous to that of the natural alkaloid. This synthetic preparation may be obtained under the name of suprareninum syntheticum.

The natural alkaloid is lævorotatory. The synthetically prepared l-epinephrin is equally as active as this, while the action of r-epinephrin is 12–15 times weaker. Recently *A. Fröhlich* found that very large doses of the dextrorotatory alkaloid so affected the circulation that even one or more milligrammes of the lævorotatory epinephrin produced no effect on the blood-pressure.

The rise in blood-pressure is caused by the extreme constriction of the smallest arteries due to direct action on the vessel walls. Secondarily, a direct and unusually powerful stimulating effect on the heart, which has already been discussed, plays a rôle in the production of this rise. The proof that the vasoconstriction is due to peripheral action is furnished by experiments in which the rise in blood-pressure occurred after the cervical cord had been severed and the spinal cord pithed, or after complete elimination of the vasomotor centres by means of chloral (*Velich, Gottlieb* [1]). Similarly, constriction of the separate vascular systems occurs after these are rendered independent of the vasomotor centres by section of their nerves (*Fr. Pick, Loewi* and *H. Meyer*). In artificial perfusion

of surviving organs the peripheral action on the vessels is expressed by retardation or even by a complete stoppage of the flow, which may occur even after maximal dilatation (*Gottlieb* [2]). The direct action on the tone of the arterial walls may be shown in an especially instructive manner by experiments on isolated circular strips of the arteries. By the use of Ringer's solution kept at body temperature, these may survive for days and maintain their irritability, so that changes in their tone may be graphically recorded (*M. v. Frey, O. B. Meyer*). After addition of epinephrin to the Ringer's solution, a distinct shortening of the strip of artery results.

This vasoconstriction is especially well marked in the arteries of the splanchnic system, but occurs also in most of the other vascular systems (*Cow*). According to *Langendorff*, the coronary vessels are exceptional in their behavior, in that in them epinephrin, instead of causing an increase in the tone, causes a diminution, as shown by the lengthening of the strip. In accordance with this, the flow of the blood through the tissues of the surviving mammalian heart is not hindered but, on the contrary, is favored by epinephrin.

Hæmostasis.—The use of epinephrin as a means of causing local anæmia and as a hæmostatic depends on its power to constrict the vessels lying at the point of application. If the drug be applied (1–1000 or 1–10,000), in dilute solution, to mucous membranes or wounds, these become extremely pale. The anæmia resulting from its application greatly increases the accessibility of cavities lined by mucous membrane (for example, in rhinological practice). In surgery, when it is important to have the operative field as free from blood as possible, epinephrin may be used locally to check hemorrhage.

In Local Anæsthesia.—Mention has already been made of the great advantage resulting from the addition of this drug to the cocaine solutions employed in the induction of local anæsthesia. It is of great practical importance that the vasoconstriction caused by epinephrin closes up the paths for the absorption of the cocaine, and thus keeps this drug at the place of its application and does not permit it to reach the central nervous system (see p. 125). As shown by *Meltzer* and *Auer* and also by *Exner*, epinephrin delays absorption from the peritoneal cavity. It is also probable that the absorption through the lymph-spaces is hindered by its actions.

Effects on Distribution of the Blood.—When epinephrin is injected directly into the circulation, the visceral vessels are especially constricted. Plethysmographic investigation shows a marked diminution in the volume of the intestines, kidney, and spleen, so that, in spite of the tremendous rise in blood-pressure, the curves from these organs move in an opposite direction from the blood-pressure curves (Fig. 30). The blood is forced out of the abdominal viscera into the heart and lungs, the vessels of which are much less affected than those of the other organs (*Gerhardt*).

The effects on the blood-pressure may be obtained in their full development by the intravenous injection of a dose corresponding to 1/100 mg. per kilo. With subcutaneous injections doses more than one hundred times as large are necessary. [The translator has found that from 0.6 to 1.0 mg. injected intramuscularly usually caused distinct effects in adult human beings, such as a rise of from 10 to 15 mm. Hg and an acceleration of the pulse, with apparent increase in the strength of the cardiac contractions. In two patients (out of a series of 30 cases) such doses caused tremendous pressor and other effects, the symptoms in one case being very alarming. The unusual effects were apparently due to individual idiosyncrasy, for these two cases reacted proportionately to smaller doses given subsequently. The translator knows of no adequate explanation for the difference in reaction to this drug which the laboratory animals and man present, but believes it important to warn against possible harm which might result from disregarding it.]

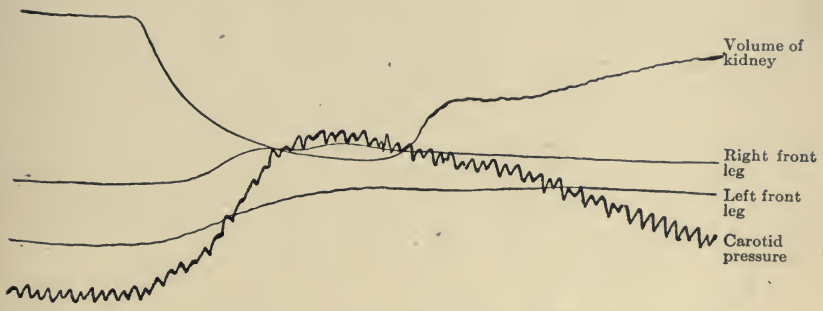


Fig. 30.—Effect produced by suprarenal extracts on the blood-pressure and on the volume of different organs (*Oliver* and *Schaefer*).

Causes of the Evanescence of the Pressor Effect.—The rise in blood-pressure following intravenous administration seldom lasts more than 1–3 minutes. This difference between the striking effects produced by intravenous injection and the comparatively slight effects of subcutaneous injections is doubtless in part due to the great instability of this drug, which is decomposed even by weak soda solutions. [Further, the local vasoconstriction must permit only a gradual entrance of the drug in the general circulation. This would result in a lessened intensity and a greater persistence of the effects of the drug when administered subcutaneously (*Miller, Halsey*).—Tr.] The rapidity with which the effects of the intravenous injections pass off may be assumed to be due in part to a rapid oxidation of epinephrin in the alkaline medium of the body fluids and tissues. In addition it is assumed that this drug acts only at the moment of entrance into the nerve-endings [?] by a "permeation pressure." If this assump-

tion is correct, the manner in which epinephrin produces its effects would be analogous to that in which muscarine (p. 248) acts (*Straub*).

Elimination.—Even when large amounts of epinephrin are administered subcutaneously or administered by mouth, only minimal amounts are excreted in the urine (*v. Fürth*).

Other Actions.—Epinephrin possesses a number of other pharmacological actions in addition to this effect on the vessels, which is, for practical purposes, its most important action. One of these is the acceleration and strengthening of the heart-beat, as a result of stimulation of the accelerator nerves. The slowing of the pulse observed at the commencement of the rise in blood-pressure is the result of stimulation of the vagus centre by the increased blood-pressure (see p. 245). The respiration during the period of high blood-pressure is affected in a peculiar manner, temporary cessation alternating with periods of deeper and more rapid breathing.

Epinephrin causes mydriasis by stimulation of the dilator pupillæ, analogous to that caused by stimulation of the sympathetic in the neck (p. 159). It causes increased secretion of the salivary glands (*Langley*), as also of the glands of the skin of the frog (*Ehrmann*), and atropine does not stop these secretions when thus excited. Further, epinephrin, even in small doses, is a powerful excitant of the contractions of the uterus (pp. 222, 229), but, on the other hand, intestinal peristalsis is inhibited by it (p. 173). The epinephrin glycosuria (*Blum, Herter* and *Wakeman*) results from the stimulating effect on the transformation of glycogen in the liver. Glycosuria produced by brain puncture and many toxic glycosurias are to be considered as resulting from a suddenly increased secretion of epinephrin (p. 419).

It is probable that the arteriosclerotic changes found in the aorta of animals which have for some time been treated with epinephrin (*Josué, W. Erb*) are not the result of the effect on the blood-pressure, but are due to a special toxic action such as is exerted by other substances of quite different nature (*Heubner*).

Seat of Action.—The question as to which elements of the vessel wall are affected by the vasoconstricting action of epinephrin may be discussed only in connection with the other actions of the drug. In this connection it was first shown by *Wessely* for the eye, and later by *Langley* and *Elliot* for all other vegetative organs, that in all of them epinephrin produced the same effects as are produced by stimulation of their sympathetic nerves, but never the same as those caused by stimulation of the other vegetative nerves. This striking parallelism renders it highly improbable that the action of this drug on the smooth muscles of the vessel walls and of the dilator pupillæ, etc., is a direct one on the muscles. It appears much simpler to attribute this action to the stimulation of the nerve-endings of the sympathetic system. A very important aid in the solution of this matter has been furnished by the above-mentioned experiments of *Langendorff* on the coronary vessels, which are not constricted by epinephrin but are dilated. According to the studies of *Maass,* moreover, vasodilators for the coronary vessels actually pass down in the accelerator nerve, while the vasoconstrictors lie in the vagus trunk. This anatomical fact, in conjunction with the action of epinephrin on the coronary ves-

sels, serves as another support of the hypothesis that epinephrin acts on the sympathetic nerve-endings and not on the muscles in the vessels, for we have no reason to believe that the muscles of the coronary vessels differ essentially from those of other vessels.

The point at which epinephrin acts, however, cannot be those nervous structures which degenerate after section of the nerve-trunks, for *Langley* found that epinephrin was still effective at a time when as a result of section of the nerve-trunk all the histologically differentiable nerve-endings had undergone degeneration. He, therefore, locates the action of epinephrin in a receptive intermediary substance lying between the nerve and the muscle. Inasmuch as we look upon the connection between the nerve and the muscle as an exceedingly intimate one, and we possess no criterion for determining what belongs to the nerve and what does not, this hypothetical receptive intermediary substance must be considered as a part of the nerve-ending.

Physiological Tests for Epinephrin.—The physiological importance of epinephrin has been established ever since it was proved that normal blood-serum contained it. Although the exceedingly small amount of epinephrin normally present in the blood cannot be demonstrated by chemical methods, it is possible to show that serum exerts the characteristic physiological effects of epinephrin, and especially is this clear with the serum of blood obtained from the suprarenal veins. This was first incontestably demonstrated by *Ehrmann,* who found that serum obtained from the suprarenal veins exerted the same mydriatic action as epinephrin when it was applied to the enucleated frog's eye. *O. B. Meyer* and *Schlayer* found that blood-serum causes the same contraction of smooth muscles of the surviving artery as is caused by extremely dilute solutions of epinephrin. In the same fashion normal blood-serum causes an increase in the tone of a rabbit's uterus "surviving" in Ringer's solution, which is an extremely delicate object for testing epinephrin (*Fränkel*), and *Trendelenburg* found that, when the blood-vessels of the frog were perfused with serum, the retardation of the flow was identical in every respect with that observed when very dilute solutions of epinephrin were perfused.

While *O'Connor* has shown that other active substances contained in the serum are responsible for part of this effect, the greater activity of serum obtained from the suprarenal veins as compared with that obtained from other organs indicates that these physiological reactions of the normal serum are at least in part due to epinephrin. Thus, the *Ehrmann-Meltzer* pupil reaction is strongly positive only when the serum from the suprarenal veins is used, and is not ordinarily produced by the serum from the carotid or jugular. In this fashion it was demonstrated that the blood from the suprarenal veins actually contained more epinephrin than any other blood (*Ehrmann*). Similarly such serum constricts the vessels of the frog much more strongly than does serum from carotid (*O'Connor*) (see Fig. 31). Moreover, blood from the suprarenal vein when injected into a second animal produces a greater rise of blood-pressure than blood obtained from other vessels (*Szymonovicz, Camus et Langlois*). The strongest evi-

dence of a physiological secretion of epinephrin is the histological fact, observed by *Arnold,* that the granular chromaffin bodies, found in the medullary cells of the suprarenal gland, pass directly from these cells into the first beginnings of the suprarenal veins.

Fig. 31 shows the course of the vasoconstriction produced in the surviving frog's vessels by serum from the carotid and by that from the suprarenal veins. That the stronger vasoconstricting effect of this last-mentioned serum is actually due to the presence of epinephrin, which has been secreted into these veins, is indicated by the destruction of the active substance if oxygen be passed through the serum for a number of hours, this ready oxidizability being characteristic of epinephrin.

Physiological Significance for the Blood-pressure.—According to *Tscheboksaroff, Asher,* and *Kahn,* it would appear that the functional activity of the splanchnic nerve depends on the internal secretion of the suprarenal glands. Bilateral extirpation of these glands is fol-

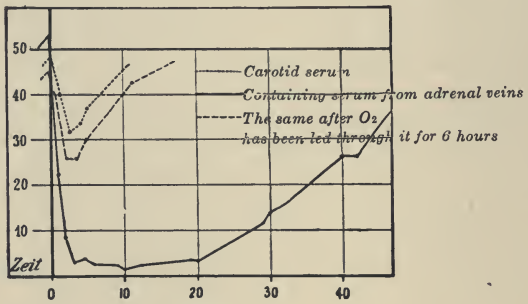


FIG. 31.

lowed by general prostration with a pronounced fall in the body temperature and progressive sinking of the blood-pressure, and is followed by death unless accessory suprarenals are present, or unless a sufficiently long period of time has elapsed between the extirpation of the first and second gland, to permit of a compensatory hypertrophy of the chromaffin tissue in other parts of the body (*Brown-Sequard, Langlois, Szymonovicz, Hultgren u. Anderson, Strehl u. Weiss*). However, it has been shown by *Biedl* that the importance of the suprarenals for the maintenance of life is not entirely dependent on the secretion of epinephrin, for the cortex of the gland also possesses vitally important functions, which perhaps consist in rendering harmless the poisonous products of muscular activity (*Langlois et Abelous*). The great physiological importance of the suprarenals is also evidenced by the uncommonly rich blood supply of these tiny organs (*Langlois, Flint*).

From what has already been said, there can be no doubt that epinephrin aids in maintaining and regulating the normal peripheral

vascular tone. It would appear that a certain apparently constant amount of epinephrin is present in the blood, and that, as there is a continuous inflow of this substance into the blood, a constant effect on the sympathetic nerve-endings is exerted, the epinephrin which has reached the cells being constantly destroyed, but that just entering them stimulating the nerve-endings (*Straub u. Kretschmer*). Inasmuch as the histological studies of *Wiesel* have shown that the medulla of the suprarenal gland and the other chromaffin tissues stand in a close developmental relation to the sympathetic system, it would appear that this system provides for the maintenance of its own stimulation by itself producing the stimulating substance.

Practical Applications.—The use of epinephrin to influence the cardiac action and the general distribution of the blood will be discussed later. It is extensively employed as a local application to mucous membranes and bleeding wounds, especially in combination with cocaine, which also has, to a less degree, a vasoconstricting effect (see p. 124).

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THE DIGITALIS BODIES are also to be numbered among the substances which cause constriction in important vascular systems by a local action. With them, too, this action is a local one in the vessel wall, for the vasoconstriction produced by them occurs after section of the cervical cord and pithing of its lower portions. Here, too, it is not possible to determine definitely which elements in the vessel wall are acted upon, but it appears justifiable to consider the action on the vessels as analogous to that on the heart, which, in point of fact, is only a more highly specialized artery. That the action of digitalis on the vessel walls is a local one, taking place in the vessel walls themselves, was indicated by the first observations made by perfusing cold- and warm-blooded organs (*Donaldson* and *Stevens, Kobert*) with digitalis substances, for in these experiments the blood stream was retarded after addition of such drugs to the perfusion fluid. As long as such evidence depended only on experiments on surviving organs, it remained questionable whether the same held good for living animals. Since that time the vasoconstricting action in the intact mammal has been definitely proved by the use of various experimental methods.

In an indirect fashion *Lauder-Brunton* and *Tunnicliffe* reached the conclusion that the vessels were constricted by observing the retarded flow of blood through the narrowed arterioles into the veins. If the heart in the intact circulation be stopped by stimulation of the vagus, the rapidity and the extent of the fall in pressure in the aorta depend on the resistance in the vessels against which the large arteries empty themselves during the persistent diastole of the heart, and if the blood path is widely opened the outflow is rapid and the blood-pressure sinks rapidly. With contracted vessels, on the contrary, this must take place more slowly. In the experiments of these authors comparison of the behavior of the blood-pressure during the stoppage of the heart induced by vagus stimulation showed an appreciably slower fall after injection of digitalis than occurred before.

Differences in the Degree of Vasoconstriction Induced in Different Organs.—A knowledge of the behavior of the different vascular systems under the influence of digitalis has been obtained by means of the

plethysmograph, as well as by the method of measuring the amount of blood passing through the separate vascular systems as described on page 242 (*Bradford* and *Phillips, F. Pick*). In these experiments it was demonstrated that after very small doses the vasoconstriction affects chiefly the visceral vessels (*Gottlieb u. Magnus*), while other vascular systems—for example, the vessels of the skin and muscles, as also the renal vessels—dilate (*Loewi u. Jonescu*). This difference in behavior is due to a quantitatively different susceptibility of the different vascular systems, which may best be demonstrated in perfusion experiments on surviving organs. Those concentrations of digitoxin and strophanthin, which when perfused dilate the renal vessels, cause a constriction of the intestinal vessels, while the vessels of the skin and muscles are entirely uninfluenced and are constricted

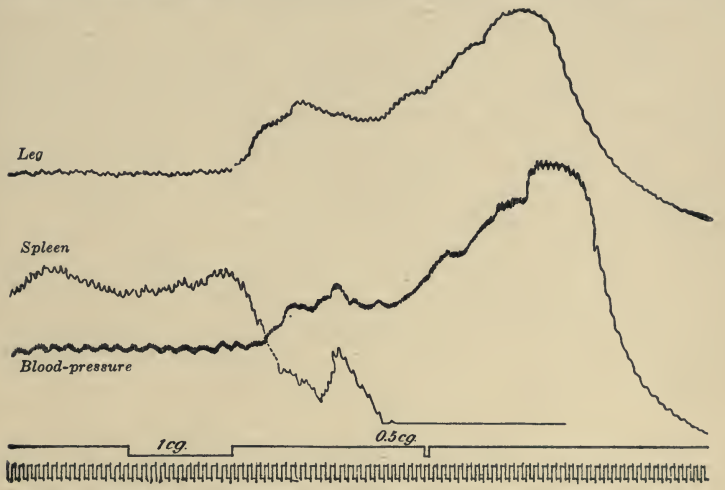

Fig. 32.—Effects of strophanthin on blood-pressure and on volume of spleen and leg.

only by much higher concentrations (*Kasztan, Fahrenkamp*). It may be concluded that in the living animal the vessels of the extremities will be dilated during the early stages of digitalis action, because the blood will be mechanically driven out of the visceral vessels when these are constricted while the vessels in the extremities are as yet uninfluenced by the drug. All these vasomotor reactions are in part caused by depressor reflexes, which cause a distinct dilatation of the vessels in the extremities in order that in them a place may be found for the blood forced out from the visceral vessels (see Fig. 32).

The behavior of the kidney vessels previously mentioned demonstrates that digitalis bodies may exert a vasodilating action which, as shown by *Loewi* and *Jonescu's* experiments on the kidney isolated from its nerves and by *Kasztan's* and *Fahrenkamp's* on surviving organs, is a direct one on the vessel walls. In the vessels of the intes-

tine almost the only action of the digitalis bodies is that of vasoconstriction.

Quantitative Differences between the Different Digitalis Bodies.—All the members of the digitalis group have a vasoconstricting action, which, however, is developed to a different degree in different members of the group, being developed in the case of digitoxin and much less so in digitalin, strophanthin, and others.

After toxic doses of these substances, but especially of digitoxin, all parts of the systemic circulation take place in the vasoconstriction, and the dilatation of the peripheral systems does not occur—or is developed only as the action passes off and the blood-pressure rises markedly. With doses causing a somewhat less intense effect, the intestinal and hepatic vessels and usually also the renal vessels are constricted, while in the periphery of the body, as well as in the brain, the blood flow is improved.

Finally, very small doses produce only a change in the distribution of the blood without rise in the general pressure, *the intestinal vessels being constricted* and the renal vessels being dilated (*Loewi* and *Jonescu*).

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PERIPHERALLY ACTING VASCULAR DEPRESSANTS

Amyl Nitrite.—Numerous drugs and poisons possess a depressing action on the vessel walls. In particular, amyl nitrite and other nitrites, in addition to acting on the vasomotor centres, cause, even in non-poisonous dosage, a demonstrable peripheral vascular paralysis.

The narcotics of the alcohol group, especially chloroform and chloral hydrate, show a similar peripheral action only in such high concentration that it is of significance only in most severe poisoning. This effect is shown in surviving organs by the great increase in the blood flow when these drugs are perfused. In perfusion experiments an effect on the vessels occurs only with a chloroform content of 0.1 per cent. (*Sherrington* and *Sowton*), and, as a concentration of from 0.06–0.07 per cent. of chloroform quickly kills by paralysis of the respiration, this peripherally induced dilatation in contradistinction to the central vasomotor paralysis is of no practical significance for the action of chloroform.

Capillary Dilators.—It is probable that toxic actions on the vessel walls are often not limited to the arterioles, but that the calibre

of the capillaries may also be affected. This has been demonstrated for the vasodilating action of arsenic and antimony, as well as for other metal salts and other substances, among which is sepsin, a very poisonous base produced by certain bacteria. The point of predilective action of these capillary poisons lies in the walls of the intestinal vessels. That this vasodilatation is of peripheral origin is demonstrated by the fact that the excitability of the splanchnic nerve for electric stimuli constantly diminishes as the fall in blood-pressure progresses (*Böhm u. Unterbringer, Pistorius*). The extreme hyperæmia of the intestines resulting from these toxic actions, the extravasations of blood, and the alterations in the capillary walls make it clear that these poisons exert an elective action on the capillaries.

The elective action which some drugs exert on special vascular systems is the basis of their therapeutic application.

Yohimbin is a good example of a drug exerting such a peripheral elective action on vessels, which occurs even after previous section of the nerves, but affects only certain vascular systems, or at least is especially pronounced in them. It causes a dilatation of the vessels in the genital organs, which may be demonstrated by the increased flow of blood through the dorsal vein of the penis. Simultaneously the vascular systems of the skin and kidney dilate, while other vessels —for example, those of the spleen—contract. The aphrodisiac action of yohimbin (p. 219) is due partly to this increased blood flow to the genital organs, and partly to an augmentation of the reflex excitability of the centres of erection (*Franz Müller*).

Caffeine also exerts a local elective action on the renal and the cerebral vessels, while the dimethylxanthines (theobromine, theocin, etc.), as well as digitalis, act in a like manner on the renal vessels. Caffeine and theobromine, and perhaps also amyl nitrite, have a specific power of dilating the coronary vessels, an action of great significance for the flow of blood through the tissues of the heart.

Vascular Alterations from Local Applications.—Aside from such elective pharmacological actions in the different vascular systems, local vasodilatations and vasoconstrictions, resulting from a direct contact of chemical substances with the vessel walls, are of considerable importance. Thus, the astringents (see p. 213), when not too highly concentrated, produce a constricting effect on the vessels at the place of application. The same substances in higher concentrations, as well as all irritants, dilate the blood-vessels locally. Further, in inflammation, local vasodilatation may be caused either by irritating substances penetrating from the exterior or by products of the pathological tissue changes. The influence of increased function is of a similar nature, for there is certainly a local cause for the increased inflow of blood which occurs during activity of an organ, caused probably by some of the products of the metabolism of the organ exerting a

vasodilatating action. It may be that the vasodilatation, which *Bier* has shown to result from temporarily cutting off the blood supply, is brought about in an analogous fashion. Finally, in this connection, it is proper to state that cold constricts while heat dilates the vessels.

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THE EFFECTS ON THE CIRCULATION AS A WHOLE PRODUCED BY DRUGS ACTING ON THE HEART AND ON THE VESSELS

The indications for the administration of drugs acting on the circulation are found in the presence of disturbances of the heart function or of alterations in the distribution of the blood, resulting from vascular paresis or vascular cramp.

Disturbances of the Cardiac Function.—The heart, as the motor organ of the circulation, has the task of driving the blood through the arterial and venous portions of the systemic and pulmonary circulations in quantities sufficient to supply the needs of all the organs. It is not able to do this—1st, if it is beating too slowly; 2d, if both ventricles empty themselves too incompletely; or, 3d, if either of the two ventricles is no longer contracting forcibly enough to expel its contents in a normal fashion. These different types of insufficient heart function lead necessarily to somewhat different results, for in case of too slow action of both halves of the heart, or in case of an equally incomplete emptying of both ventricles, there will result only a dangerous retardation of the blood flow in both circulations. On the other hand, in case one ventricle is unable to empty itself completely, the distribution of the blood throughout the body will become abnormal and stasis will result.

In an acute anæmia from hemorrhage both sides of the heart receive and pump out too small a quantity of blood. Also in *enfeebled conditions of the heart,* such as may be caused by numerous exogenous poisons, as well as by the toxins of infection, the contractions of both ventricles become equally incomplete and feeble. In both cases the skin becomes pale and the extremities cold and the brain is poorly supplied with blood. As this organ is extremely sensitive to disturbances of its circulation, interference with its blood supply quickly results in a feeling of faintness. While the other organs also suffer more or less as a result of the retardation of the blood flow, the heart especially suffers on account of the insufficient circulation in the coronary vessels.

Stasis.—When one ventricle is beating feebly while the other continues to function normally, or when the efficiency of one is im-

paired to a greater degree than that of the other, quite different conditions arise. If, for example, the left ventricle contracts incompletely, on the one side, too little blood flows into the aorta and, on the other, the auricle is unable to empty itself completely into the ventricle on account of the residual blood left there at the end of the incomplete systole. The blood, therefore, accumulates first in the left auricle and then in the pulmonary vessels. If, now, the right heart continues to pump out blood in the same amounts as before, the left heart must soon become dilated and the stasis in the pulmonary vessels will increase, dyspnœa and, with marked stasis, œdema of the lungs resulting.

If it be the right ventricle which is affected, the blood accumulates in the right auricle and the great veins, and especially in the capillaries of the whole portal system, which is immediately affected by every rise in pressure in the vena cava. Congestion of the liver, impaired renal circulation with its resulting oliguria, and stasis in the vessels of the intestines result, and ascites may develop.

Effects on the General Blood Flow.—With one of the ventricles contracting inefficiently, the arterial portion of its vascular system is inefficiently filled, and the blood accumulates and remains in the veins from which it receives its supply. This blood is, as it were, removed from the circulation, so that the blood flow in all the tissues is diminished. With marked venous stasis the capillaries are also overfilled. Cyanosis results when too little blood flows through the lungs.

Circulatory Insufficiency Due to Cardiac Disease.—Such conditions arise both in disease of the myocardium and of the valves, unless the resulting interference with the circulation of the blood is more or less completely compensated. The first compensatory change is brought about by hypertrophy of the muscles of the overfilled and weakly contracting part of the heart or of the heart chamber next involved, which is thus enabled to pump out the blood in sufficient amounts and with sufficient force to overcome any unfavorable conditions in the circulation. When, as a result of progressive valvular or myocardial disease or of impaired nutrition of an overtaxed heart, compensation is finally broken down, stasis develops in the pulmonary or systemic systems or in both, and its symptoms—dyspnœa, cyanosis, congestion of the liver, oliguria, ascites, œdema, etc.—result. Under these conditions, digitalis is the sovereign remedy.

THEORY OF THE ACTION OF DIGITALIS

The separate pharmacological actions of digitalis having been discussed, it is now in order to consider the general effects produced by these separate actions. As stated in previous sections (see pp. 264–5), the drugs of this group enable the heart to accomplish more work with each contraction, and proofs have been presented (see p. 286) that thus the minute volume of blood pumped is, under certain condi-

tions, increased. It has also been demonstrated that, simultaneously with such alterations of the heart function, vasoconstriction occurs in various vascular systems, and that these primary and direct digitalis actions tend to bring about a rise of blood-pressure. A third digitalis action—that is, a retarding of the cardiac action, which appears in the early stages—works in opposition to these two blood-pressure raising actions (see p. 245).

The retardation of the pulse is one of the first of the digitalis effects to appear, and it is so well developed after therapeutic doses of the drug that *Traube* originally considered this the most important result produced by therapeutic doses. He also recognized it as due chiefly to a central stimulation of the vagus, which view is held by many at the present day. *Lenz's* and *Traube's* own later recognition, as a result of experiments on animals, of the great rise in blood-pressure caused by effective doses led to his abandonment of this view, and he concluded that the slowing of the heart action was simply one of the symptoms resulting from the general action on the circulation, a symptom, moreover, of considerable importance, for it supplies a convenient means for determining the degree of digitalis action which has been produced.

Rise of Blood-pressure.—With the discovery of the rise in blood-pressure which in normal animals is caused by digitalis, the doctrine of digitalis actions entered on a new phase, and this action has since then exerted a preponderating influence on the views of its pharmacological action. The therapeutic effects of the drug have been attributed to the improvement of the blood-pressure and the better filling of the arteries resulting from its use, and indications for its employment have been sought in conditions of low blood-pressure. However, as will soon be seen, modern clinical observations force an abandonment of this view, so that the explanation of its curative action is to be found not so much in a raising of the blood-pressure as in an alteration of the distribution of the blood.

However, in order properly to understand the complex actions of digitalis and their influence on the blood-pressure and the distribution of the blood throughout the body, it is best to start with a consideration of the augmentation of blood-pressure which in animals regularly results from administration of toxic doses.

The *increased "pulse volume"* of the heart will of itself tend to raise the aortic blood-pressure. This has been demonstrated in the most indisputable fashion by *Bock*, who, making use of his "heart-lung" circulation, found that after injections of digitalis bodies the blood-pressure quickly rose, although at first the heart-rate was unchanged (see Fig. 33 and p. 240). Such results prove that increase of the pulse volume of the heart is, at any rate, one of the causes of the increased blood-pressure.

The augmentation of the pulse volume caused by digitalis may be

due to a more extreme relaxation of the heart without any increase of the contractions, or it may be that the ventricle, which was not contracting maximally, under the influence of the drug is enabled to contract more completely than before. Both factors may work together, but much speaks for the view that a more complete contraction is the chief factor in increasing the pulse volume of the heart. For example, in *Bock's* experiment "the rise in blood-pressure was less strongly pronounced in strongly beating hearts and more pronounced in feebly contracting ones." Under normal conditions, the contractions of the mammalian heart are not complete,—that is, it does not contract to such a degree as completely to obliterate the ventricular lumen. Moreover, as a result of any damage done to it by such manipulations as are involved in exposing the heart or in the preparation of the great vessels or in similar procedures, its contracting powers are further impaired. Therefore, at the end of each systole the ventricle retains a certain amount of blood. In *Bock's* experiments, when the contractions were relatively complete, approximating

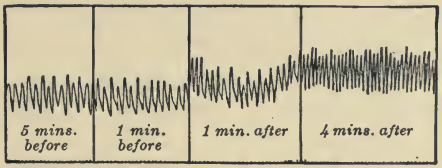

FIG. 33.—Blood-pressure in "heart-lung" circulation before and after digitalis body.

the normal, the digitalis could improve the contractions to a slight degree only. If, however, the heart were beating poorly and the contractions were abnormally incomplete, the favorable influence exerted on the contractions was more pronounced and the blood-pressure rose markedly.

The "Langendorff" isolated heart always contracts less completely than a heart *in situ*, for the amount of blood flowing through its vessels is always far smaller than that circulating through the vessels of the heart in the intact circulation. It is probably for this reason that digitalis exerts such a favorable influence on its contractions (*Magnus u. Sowton*).

Cushny's observations on the intact circulation of dogs and cats agree with this conception. Using a cardiometer (a plethysmographic instrument), he estimated the amount of blood forced out during each systole, and found that digitalis caused a distinct increase of the pulse volume of the heart, which, in his experiments, was undoubtedly somewhat weakened. This was graphically recorded, and must be attributed chiefly to an influence on the extent of the contractions, for the curve showed this to be distinctly increased while the relaxation during diastole was but slightly influenced.

The rise in blood-pressure is, however, not only the result of augmentation of pulse volume of the heart, but is also in part the result of vasoconstriction.

Tigerstedt, by the use of his Stromuhr (current clock), determined the amounts of blood pumped into the aorta during the unit of time, before and after the administration of digitalis, recording the carotid pressure at the same time, and found that, as a rule, the "second volume" of blood expelled by the heart increased simultaneously with the rise in blood-pressure which followed the injection of digitalis. However, in some cases where the pressure rose markedly, the "second volume" of the blood expelled was not increased, and in all cases it was diminished again at a period when the blood-pressure was still rising.

The analysis of the "pressor" effect thus shows that the influence of "heart work," or "heart performance," and the constriction of the more important vascular systems go hand in hand. As a result of the joint effect of these two factors, the blood-pressure would necessarily be raised under all conditions, were it not for the fact that digitalis and its congeners exert a third fundamental action on the circulation, that of pulse retardation, which, in the first stages of the digitalis action, acts in opposition to the two other actions of the drug. In experiments on animals, the slowing of the heart thus caused may be so pronounced as to result in a diminution in the volume of blood pumped out per minute, in spite of the increase in the amount pumped by each contraction. It may thus happen that at first the blood-pressure does not rise (after injection of digitalis) so long as the heart rate is slowed, but it always rises if the vagi be cut or when at a later period the heart becomes insusceptible to the inhibitory influence of the vagus.

Regulatory Action.—Still a fourth fundamental action of digitalis, the regulation of arrhythmic cardiac action, may be demonstrated in both the intact circulation and the artificially perfused mammalian heart as well as in the "heart-lung" circulation. This action is present, however, only in the early stages,* and, as a matter of fact, *in the later stages irregularity of the pulse occurs and is a typical symptom of the*

Toxic action of digitalis, developing some time before the blood-pressure, usually quite suddenly, dropping to zero as the heart dies. If the complex fashion in which these different pharmacological actions of digitalis mutually affect each other be considered, the course of the

* [This sweeping statement is correct only in so far as it refers to experiments in animals or in certain clinical conditions. As a matter of fact, in various clinical conditions, such as auricular fibrillation very often and premature systolic arrhythmias occasionally, a decided improvement of the regularity of the heart action is an expression of the full and desired therapeutic action of digitalis and its congeners (see translator's notes, pp. 266, 300).—Tr.]

blood-pressure curve (Fig. 34) may be understood. Two stages may be differentiated:

1. A stage during which the heart action is strengthened and slowed, which may be called the therapeutic stage, for these early actions are alone of therapeutic value. Regulation of the heart action, augmentation of the pulse volume of the heart, constriction of important vascular systems with simultaneous compensating dilatations in others, and slowing of the pulse, characterize this stage. The blood-pressure, depending on the extent to which the pulse is retarded, may rise slightly or remain constant [or may fall somewhat.—Tr.].

2. A toxic stage in which the blood-pressure, in spite of persisting pulse retardation, and later during a sudden acceleration, continues to rise. In this stage the vasoconstriction is chiefly responsible for the rise in pressure, for the work performed by the heart is at this time lessened. Finally the heart action becomes irregular and the blood-pressure falls.*

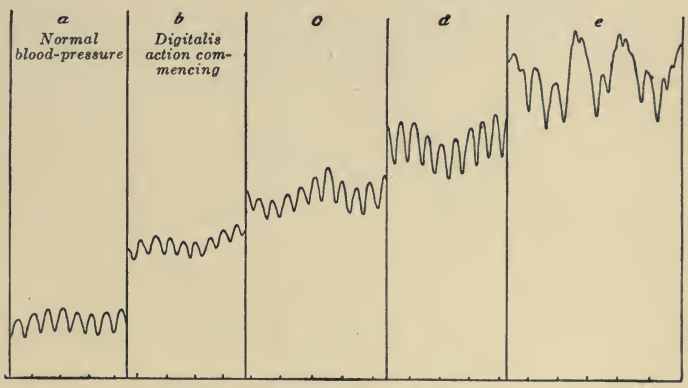

Fig. 34.—Blood-pressure curves showing the effects of digitalis in a dog (*Williams*).

It is thus seen that in the first stage of digitalis action, the only one having a bearing on its therapeutic usage, the blood-pressure is not necessarily raised. Obviously the conditions in the healthy man are similar. *Fränkel* observed in healthy persons, used as test objects, a rise in blood-pressure only after the compensating pulse slowing had been prevented by administration of atropine. Moreover, *in patients in whom stasis is present the curative action of digitalis usually manifests itself without causing any augmentation of blood-pressure.* We owe the establishment of this important fact to the development of methods for the bloodless determination of blood-pressure (see p. 236),

* [The irregularity in the heart's action at this stage may be the result either of more or less complete heart-block, or of premature systoles (due to increased irritability of the ventricle), or to auricular fibrillation (due to the digitalis), or to combinations of two or all of these factors.—Tr.]

for by their employment it has been shown that digitalis may remove conditions of stasis without causing a rise in pressure (*Sahli, Lang*). This is also the case after intravenous injection of digitalis or similar drugs (*Fränkel u. Schwartz*), the observations made when the drug is thus administered being especially valuable because the effects on the circulation ensue with the same rapidity as in experiments on animals and consequently may be exactly determined.

Altered Distribution of the Blood.—Inasmuch as digitalis is able to remove conditions of stasis without necessarily markedly influencing the blood-pressure, the improvement of the circulatory function cannot be attributed to an augmentation of the arterial pressure. The curative action of these drugs under such conditions should rather be attributed to the fact that the abnormal distribution of the blood and the stasis are replaced by normal conditions. In order to understand this more completely it is necessary to observe THE ACTION OF DIGITALIS IN PATIENTS SUFFERING FROM HEART DISEASE.

While it is true that the pharmacological actions of these drugs are fundamentally the same in the normal and pathological circulations,* in the presence of pathologically altered function the results produced by these actions present themselves quite differently. It must be quite clear that the conditions obtaining in cases of cardiac insufficiency are especially calculated to render the very first stages of digitalis cardiac action beneficial, for here the drug is acting not on a ventricle beating with the normal optimal efficiency but on one contracting inefficiently. Any disparity in the performance of the two ventricles will be removed by improvement of the function of that portion of the heart which is not working well. As a result the venous stasis will be relieved by a shifting of the blood from the venous side of the circulation over to the arterial portion.

Under pathological conditions the slowing of the pulse produces a distinctly more beneficial result on the total performance of work by the heart than is the case under conditions of health. While in the healthy heart digitalis reduces the pulse below the normal, in cardiac disease, whenever it produces its desired effect, it usually brings it back to the normal. The effect of such action on the circulation is entirely different in the two conditions, for, as shown by the investigations of *Frank* and *von Hofmann*, the heart beats with maximum efficiency when beating at its normal rate. The simple inspection of the accompanying diagrammatic curves, representing the changes in the ventricular volume during a cardiac cycle (Fig. 35), demonstrates that much less blood is expelled by heart-beats following each other with abnormal rapidity than is the case when the rate of the heart action is about normal.

* See translator's note, pp. 266, 300.

The ordinates in the figure represent volumes, the abscissa, time, and the highest point of the curve corresponds to the most complete contraction. The amount of blood expelled at each period of the systole, or the amount received during the diastole, is represented by the difference in height of the ordinates. With a normal frequency of the heart action, the new contraction of the heart starts at that point of the volume curve *A-B* which corresponds to the maximum amount of blood which may be expelled by the ventricle. During pathologically rapid heart action, on the other hand, the diastolic relaxations become incomplete, because at the moment of the recurrence of a new contraction—for example, at the height of lines *b* and *c*—the heart has had time for only incomplete relaxation when the next contraction begins.

A lessened frequency of the pulse, therefore, permits of better contraction of the whole cardiac cycle and of better refilling of the ventricles. When beating at a moderate rate, the heart not only performs more work in the unit of time than it does when beating rapidly, but it performs this work more economically, as it can utilize its energy more completely.

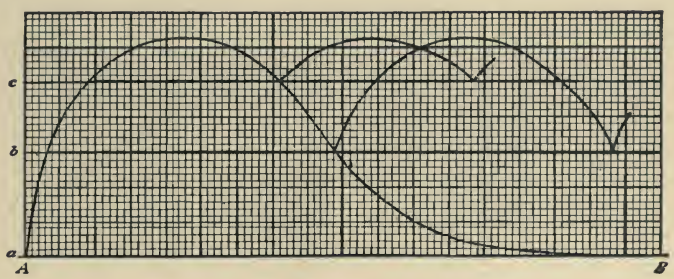

FIG. 35.

The lessening of the pulse frequency acts, therefore, in the same sense as the more powerful contraction of the heart. For this reason it would appear that digitalis should bring about a rise in blood-pressure, especially in conditions of stasis. Actually, however, in cardiac disease, blood-pressure in the aorta is not materially increased by digitalis, in spite of the important increase of the volume per second which is expelled by the heart. This must be due to the peculiar conditions obtaining in the pathological circulation. In all probability important vascular systems become more dilated than they were before the stasis was relieved.

This view agrees with all that has been ascertained about the behavior of the vessels in conditions of stasis. In conditions of cardiac insufficiency, as a rule, the arteries exhibit a tendency to become constricted, their stronger tonus keeping the blood-pressure high. The cause of this vasoconstriction has not yet been fully cleared up, but certainly a rôle is played here by the carbonic acid which is present in abnormal amounts in the blood. Moreover, the absence of the reflexes which ordinarily keep the peripheral resistance low when the vascular system is well filled must be of importance. However that

may be, in cardiac insufficiency a sort of vascular cramp must be assumed to be present before the action of digitalis develops. As the circulation in the lungs improves under the influence of digitalis, the asphyxia, and with it the abnormal contraction of the vessels, passes off, and, as the heart is now once more filling the systemic arteries more completely, the depressor nerve again exerts its function as a safety-valve and dilates the previously constricted vessels. *It is thus evident that under such pathological conditions digitalis acts indirectly as a vasodilator.*

Does Digitalis Under Clinical Conditions Cause Vasoconstriction?—As, on the other hand, experiments on the normal animal have shown that digitalis exerts a direct constricting action on the vessels, the question arises: Does this occur after therapeutic doses or only after the administration of those larger toxic doses which produce augmentation of the blood-pressure?

In animal experiments, at least, the vasoconstriction in the portal systems and the dilatation of the renal vessels do not occur later than those on the heart, but at the same time, and are observed after doses producing hardly any effect on the blood-pressure. As perfusion of surviving organs permits of comparing the relative susceptibility of the vessels and the heart, it has been shown by this method that solutions of digitalis and of strophanthin, which may be perfused for a long time through the heart without harming it, promptly constrict the intestinal vessels and at the same time dilate the renal arteries (*Fahrenkamp*). In these experiments the effects on the vessels and the improvement of the contraction of the heart, with an increase of its "minute volume," occur at the same time. From such experiments, *it seems probable that in the living body also the dilatation of the renal vessels and the contraction of the intestinal vessels occur during the same stage of the pharmacological action as do the favorable effects on the cardiac function.*

Recent observations made on normal men by *O. Müller, Vagt,* and *Eychmüller* do not agree with this view. These authors were not able to demonstrate a constriction of the intestinal vessels after intravenous injection of digitalis bodies, although a distinct but slight effect on the heart was produced. As these doses also produced no diuretic effect, they therefore were not large enough to cause dilatation of the renal vessels in healthy subjects. It was not possible to observe the behavior of the intestinal vessels in patients with cardiac disease, in whom the same doses produced pronounced effects on the heart and increased diuresis. It appears to the authors (*G.* and *M.*), however, that the conditions obtaining in a pathologically disordered circulation are too complicated to justify a conclusion that vasomotor changes do not occur in internal organs simply because the plethysmographic curves obtained from the arm fail to indicate their occurrence.

In cardiac disease the effects produced on the heart function appear

to be the most essential reason for the usefulness of these drugs, but the vasoconstricting action on the vessels of the intestines and liver also appears to be beneficial. The clinical picture observed in patients, in whom stasis due to cardiac disease is present, indicates, as emphasized by *Sahli*, that not only the great vessels but also the whole portal system is over-distended with blood. Vasoconstriction in this system—which, as is well known, may contain extremely large amounts of blood—can be of great assistance to the heart by starting this stagnating blood to flowing again so that it may aid in filling other vascular systems.

Against the view that the vascular actions of digitalis play any part in causing the benefits obtained from its therapeutic employment, objection has been raised, on the assumption that a vasoconstriction entails the burdening of the heart with a great task, and that therefore drugs of the digitalis group would be poor agents to use to aid a struggling heart if they increase the resistance against which the heart must expel its contents. This objection would be justified if these drugs, in therapeutic dosage, caused a general vasoconstriction. However, *small therapeutic doses affect practically only the vessels most susceptible to their influence, namely, those of the portal system.* As the blood is thus forced from the vessels of the intestines and liver into other vascular systems, which are not constricted by these doses,—for example, into the renal vessels, which are in fact dilated under the influence of digitalis,—the resistance of the total cross-section of the vascular tree need not be increased to an extent greater than is compensated for by the increased efficiency of the heart action.

Behavior of the Renal Vessels.—A second weighty objection rests on the behavior of the urinary secretion, for the increased diuresis speaks against any vasoconstricting action in the kidney, for any diminution of the blood flow through the kidney ordinarily causes diminished secretion. However, *Loewi* and *Jonescu* have shown that the renal vessels, in contradistinction to the vessels of the intestines, are not contracted but are dilated by the small doses of digitalis, or other members of this group, which correspond to those used in therapeutics. Very small doses of strophanthin, while causing a constriction of the intestinal vessels, produce little or no change in the blood-pressure, but still they stimulate diuresis. Moreover, the surviving renal vessels are dilated by the digitalis bodies in concentrations which constrict the intestinal vessels, and are constricted only by much stronger solutions (p. 287). The renal vessels are, therefore, one of the vascular systems which profit by the forcing out of the blood from the primarily constricted portal system.

From the above it would appear that *vasomotor effects may well play a rôle in the therapeutic use of digitalis.* As a result of the fact that, if stasis be present, the vasoconstricting action is more pronounced in the vessels of the portal system, a new redistribution of

the blood occurs, the blood being forced along not only from the veins into the arteries of the general circulation but also from the passively congested liver and intestines into other parts of the body.

In still another way the actions on the vessels may be of moment. Recent investigations (*Hasebroek, Grützner*) make it probable that the active rhythmic contraction of the smallest vessels contributes to the maintenance of the circulation. If this be true, the action of digitalis on the vessels may be of value as aiding in forcing the blood along in the capillaries, and the absorption of œdema may thus be facilitated.

A consideration of the conditions obtaining in pathological disturbances of the circulation thus leads to the following conception of its beneficial therapeutic action: *Digitalis enables a ventricle, which has become insufficient, again to contract more completely, and brings about a better flow of blood through the organ. This results in the disappearance of the vasoconstriction in the large vascular systems which, in spite of existing stasis, has maintained the blood-pressure. With the restoration of an efficient functional activity of the heart, the conditions of blood-pressure and blood flow return to the normal, and the blood which has collected in the venous systems is brought back again into the arterial systems. The contraction of the vessels of the intestines and liver forces out the blood collected there, so that the vessels in other organs—e.g., the kidney, brain, and peripheral parts of the body—are better filled, and the abnormal distribution of the blood is replaced by a normal one.*

[As first shown clinically by *McKenzie* and as emphasized by all the more recent careful studies of the effects of digitalis in patients with cardiac disease, the action of digitalis in lessening or abolishing the conductivity of the bundle of His (pages 266 and 294) is the most decisively beneficial effect produced by it in a large group of cases. It is this power of protecting the ventricle from a constant shower of stimuli arising in the fibrillating auricle, which is chiefly responsible for the almost miraculously curative action of the drug in many cases of threatening failure of the circulation.—Tr.]

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PRACTICAL EMPLOYMENT OF DIGITALIS

Digitalis leaves were formerly used in England as a household remedy for dropsy, but had been forgotten when *Withering,* in the last half of the eighteenth century, recognized their great value, and, after using them for a decade, published his results. As has long been known by clinicians, though only comparatively recently definitely demonstrated by physiological assay, the pharmacological activity of the leaves is very variable, and differs with the locality from which they have been obtained, the age of the plants, and the time elapsed since they have been gathered, as well as with the conditions under which they have been prepared and preserved. This variation in the activity of different digitalis preparations, the importance of which has only recently been recognized, is perhaps the chief reason why this drug, even after extensive use for 125 years, is not yet generally administered according to generally recognized and fully established rules, but is ordinarily employed by the individual physician according to his own subjective experience and impressions. Preparations assayed by physiological tests are now obtainable and widely used.

Active Principles.—Among the definitely constituted active principles of the digitalis leaves are the almost insoluble crystalline *digitoxin,* first prepared by *Schmiedeberg* (the digitaline nativelle of the French), and the rather insoluble *digitalin* of *Schmiedeberg* and *Kiliani.* In addition, digitalis leaves contain water-soluble glucosides named, by *Schmiedeberg, digitaleins.* All these substances possess typical digitalis actions, digitoxin being the most active and powerful. In the leaves they probably occur chiefly in the form of combinations with the tannic acid, which in pure form are insoluble in water but are readily soluble in dilute alkalies.

In addition to these useful pure principles, there are also present a number of *digitonins,* which are saponins and do not possess the physiological actions of the digitalis bodies. On account of their local irritating actions, they often play a part in the causation of digestive disturbances which not infrequently develop in the therapeutic use of digitalis. [They also probably aid in bringing the insoluble and useful active principle into solution, as, for example, in the infusion.—Tr.]

Digalen is a proprietary preparation of the active principles dissolved in water and glycerin. According to *Cloetta,* it contains a soluble digitoxin, but according to *Kiliani* only an impure digitalein. [*Hatcher* has shown that the claims made for the activity of this preparation are greatly exaggerated, its strength being only that of a standard tincture. In laboratory tests made by the translator, this preparation has been found to be of inconstant strength, probably on account of deterioration on keeping for any length of time.—Tr.]

Methods of Assay.—The digitoxin contents of digitalis leaves may be determined chemically, but it does not run parallel with the physiological activity of the leaves, for the leaves are much more active than can be accounted for by the digitoxin present (*Ziegenbein, Focke*). As the other active principles cannot be estimated by chemical methods, physiological methods are the only ones available

for the determination of the activity of the leaves or the galenic preparations made from them.

Necessity of Assay.—The determination of physiological activity of these drugs is necessary because it varies so greatly in different specimens and in the different preparations made from them. *Ziegenbein* found differences of 100–200 per cent. in the activity of the leaves gathered the same year but coming from different localities. Of still greater significance is the deterioration which takes place in the course of a year in leaves preserved according to the directions given by the pharmacopœia (*Focke*). At times this amounts to a loss of 25 per cent. of their activity. It is thus easy to understand the great variations in the activity of different galenic preparations which with the tincture may amount to as much as 400 per cent. (*Fränkel*[1]). There consequently is no other drug where it is more important to substitute for preparations of uncertain therapeutic activity those of known efficiency or pure substances of constant composition. Only thus can the therapeutic use of the drug become more accurate. [Not only the leaves but also the galenic preparations deteriorate on keeping. As is widely known, this is especially true of the infusion, which deteriorates with such rapidity that it should be used only when freshly prepared. The fluidextracts appear to deteriorate but slowly. The translator found a deterioration of but 30 per cent. in a fluidextract which had been kept for three years in his laboratory.—Tr.]

The *physiological assay* of digitalis and its preparations may be made with sufficient accuracy for practical purposes by determining the minimal dose which stops the heart in systole 35–40 minutes after injection into the lymph-sac of the frog (R. temporaria).

Employment of their pure active principles would be another way to secure exact dosage for the drugs of this group, which, besides the active principles present in the digitalis leaves, includes a number of substances, chiefly glucosides, derived from different sources. From a practical point of view the different *strophanthins* are the most important of these.

Of these there are at least two known and well characterized,—one known as *Strophanthin Böhringer*, or *Strophanthin Merck*, which is amorphous and is derived from *Strophanthus kombé* or *Str. hispidus*. The other, *G-Strophanthin* * (*Str. Thoms*), is crystallizable and is obtained from Str. gratus. These strophanthins are readily soluble in water, as are *convallamarin* (from Convallaria majalis), *helleborein* (from the different species of Hellebore), *adonidin* (from Adonis vernalis), and the alkaloid *erythrophlein*. Strophanthin has proved especially suitable for intravenous administration. The other substances named have thus far acquired no particular practical importance.

A number of *other glucosides of the digitalis group* are present in various arrow-poisons, but they possess chiefly a toxicological interest. Such are, for example, echuyin (from a West African arrow-poison, antiarin (from Antiaris toxicaria), and euonymotoxin (from Euonymus atropurpureus). A non-crystallizable glucoside with digitalis actions, *scillain*, is the active principle of squills (from Scilla maritima), a drug formerly much employed.

Differences in the Actions of Different Digitalis Bodies.—The pharmacological actions of these different pure principles are by no means identical, for, although they all act on the same elements in the various organs,—*i.e.*, have the same seats of action, and exert a qualitatively similar pharmacological action,—more refined pharmacological analysis has shown many rather important quantitative

* [Ouabain is synonymous with G. Strophanthin.—Tr.]

differences, not only in their actions on the cardiac muscle and ganglia, but also in their vasomotor actions, these being more pronounced,—for example, with digitoxin than with the others (*Gottlieb u. Magnus*). The power of slowing the heart is another action which is possessed in varying degrees by various members of this group (*Kochmann*).

Of greater practical importance are the differences manifested as regards the *local irritant action* in the stomach, and, above all, in connection with their *absorbability* and their *excretion*. In this last-mentioned connection the soluble strophanthins and the insoluble digitoxin are especially contrasted. In general, those substances which are soluble in water act more promptly than those which are insoluble in water.

Cumulative Properties.—The different members of this group also differ from one another in respect to their so-called cumulative actions, although all of them exhibit the peculiar pharmacological behavior that, once their effects have been obtained, the effects persist for a considerable time. Obviously these substances are stored up in the heart. The degree and duration of their action depend on the amount thus stored up, the relatively long-continued action of single doses being explained by the fact that, once this combination of the drug with some as yet undetermined elements in the heart has taken place, it is but slowly broken up again. By continued administration of new doses the heart continues to absorb larger and larger amounts, and, as a result of the continued absorption, in the course of several days the physiological action may be developed to the desired degree.

With all the drugs of this group, still further administration may lead to a so-called cumulation, due to an accumulation of the drug in the heart in amounts larger than is desired. The persistence of the action is quite independent of the rapidity with which it develops, for a fairly lasting effect may be obtained immediately after the intravenous injection of an efficient dose of strophanthin, or much later by the oral administration of digitalis leaves, which ordinarily produce the typical effects on the circulation only after 24 hours, or even much later. However, the different digitalis bodies show marked differences in the degree and intensity of this lasting action, and these are of decisive importance for the occurrence of cumulation, as this depends on the summation of the actions of new doses with the persisting actions of the earlier ones.

The symptoms of cumulation are similar to those resulting from the administration of single toxic doses. The first are usually nausea, vomiting, and diarrhœa, succeeded in more pronounced cases by alarming retardation and arrhythmia of the pulse. The sudden change from a slow to a rapid pulse seen in animals poisoned by digitalis may occur, but not necessarily so even in most severe poisoning in man.

The vomiting, which occurs in cumulation, is a symptom produced by the drug after absorption, and is not to be confounded with that due to local irritation of the stomach, which often occurs in susceptible individuals after the first doses of digitalis bodies. This local irritation in the alimentary canal is caused not only by the useful active principles but also by the digitonins, the saponin-like constituents of the digitalis leaves.

Differences in Liability to Cause Cumulation.—Comparative investigations in animals have shown that the circulatory effect develops a few hours after the subcutaneous injection of strophanthin, while after injection of digitalis or digitoxin a much longer period elapses. On the other hand, the effects of strophanthin last a much shorter time than those of digitalis or digitoxin. The effects of this last-named glucoside are especially persistent, so that the interval between doses must be longer when it is used, if cumulative effects are to be avoided (*Fränkel*[2]). Digalen (see p. 301) also has a well-developed cumulative action (*Fränkel*[3]). This property of causing cumulative effect is, however, necessarily present in any drug possessing the typical digitalis actions and is essential for securing the desirable lasting therapeutic effects. Therefore, cumulative action may always result from continued administration of any member of this group.

Principles Governing the Dosage and Choice of Preparation.—In the clinical employment of digitalis, the attempt should be made to administer doses only large enough to secure the necessary lasting effects without causing the symptoms of cumulation to appear. The use of physiologically assayed preparations is the best means of accomplishing this. [Very frequently, however, as emphasized by *McKenzie,* the desired effect on the heart may be obtained only by doses which also cause nausea and vomiting. The danger from the cumulative action of digitalis has been generally over-emphasized by pharmacologists and by many clinicians.—Tr.]

The employment of the pure active principles has thus far not been widely favored in Germany, but in France digitoxin is much employed, in spite of its pronounced tendency to cause cumulative effects (*Marx, Zeltner*). Digitalin would appear to possess insufficient physiological activity for practical therapeutic administration. [Probably because usually used in too small doses.—Tr.] Besides this, it is decomposed in the stomach to a considerable and indeterminable extent (*Deucher*). Although the strophanthins are so efficient when administered intravenously, they are but moderately active and the effects produced by them are not lasting when they are administered by mouth. [This is perhaps in part due to the fact that they are excreted by the kidney more rapidly than they are absorbed from the alimentary canal.—Tr.]

The curative effects obtained by the use of digitalis are the result of the combined actions of the various substances contained in the leaves. As these substances exhibit marked differences from one

another in the character of their actions, in their rates of absorption, and in the persistence of their actions, it is very possible that the advantages claimed for the leaves or their preparations are due to their containing this combination of substances. Until these conditions are more thoroughly comprehended from a pharmacological point of view, it is, as a rule, therapeutically correct to give preference to the oral administration of the leaves or their galenic preparations.

The DOSAGE OF DIGITALIS leaves and of their galenic preparations varies with the length of time that the drug is to be administered. The total amount administered during the whole treatment is much more important than the size of the individual doses. This is so because of the slow absorption of the active principles and their accumulation in the heart, as well as because of their characteristic power to produce somewhat lasting effects. (Maximal dose 0.2 gm., 1.0 gm. per diem.) As a general rule, three or four doses of 0.1 gm. each of a good active digitalis powder per diem may be given, and such administration may be persisted in for three or four days, but in such dosage not for a longer period. [Much larger doses, such as 4.0–8.0 c.c. of the tincture, may be given every 24 hours for several days without danger, if the patient is kept quiet and under careful observation. In fact, at times it is only by the use of such doses, or even larger ones, that the desired beneficial actions may be obtained.—TR.]

If the full therapeutic effect is obtained on the second or third day, most competent authorities advise its discontinuation for a time or a diminution of the daily dose. In this way the cumulative action is most surely avoided. Other observers believe that the good effects of a digitalis cure are more lasting if the administration be continued, even after the appearance of the desired actions, until from 2.0 to 2.5 gm. in all have been taken. Others advise the continued administration of smaller doses, about 0.1 gm. per diem, which can be taken for a long time without the development of cumulation. [As a matter of fact, the dose for each case must be determined by trial.—TR.]

The *infusion* of digitalis is preferred by many physicians, but is *very unstable* (*Loewi*) and is weaker and more uncertain in its action, because, according to the care with which it is prepared, varying portions of the active principles may be extracted from the leaves. On the other hand, it is claimed that the infusion is less likely directly to irritate the stomach, perhaps because it contains only a smaller amount of the active principles, but also perhaps because fewer of the contaminating substances are extracted from the leaves. Similar advantages may be possessed by other extracts,—for example, the quite stable dialysate,—as well as by the tincture, which is so often preferred for long-continued use.

Digipuratum.—During the preparation of digipuratum, an extract of purified digitalis, the elimination of inactive contaminating substances is carried still further, for as much as 90 per cent. of the solid constituents may be removed from alcoholic extracts of the leaves without diminishing their physiological or therapeutic activity. It would appear that this preparation is especially free from digitonin and other saponin-like components of the crude drug, for it represents in almost pure form the combinations of tannic acid and the active glucosides. These are insoluble in the stomach, and therefore irritate its mucous membrane but slightly, while, in the alkaline intestinal contents, they are readily soluble, and therefore relatively easily absorbed. According to some observers (*Höpffner*), this preparation disturbs the stomach less than all other digitalis preparations of equal physiological activity.*

Intravenous Administration.—When in critical cases it is important to obtain the effect of digitalis more rapidly than is possible by oral administration, intravenous administration may, with great advantage, be employed. The subcutaneous or intramuscular injection of all active digitalis preparations is painful, and, if really effective doses are thus administered, marked local irritation results, while the subcutaneous injections of weaker preparations or of relatively high dilutions possess no advantage over their administration by mouth [except that at times the stomach rejects all medication administered orally. In such cases the rectal administration of relatively large doses in moderate dilution may be followed by gratifying results.—Tr.].

After intravenous injection of suitable preparations of digitalis, the effects on the circulation may manifest themselves within a few minutes, and the favorable action is usually fully developed at the end of an hour and often lasts for a long time [12 to 24 hours or more.—Tr.]. Only pure substances readily soluble in water should be used for this purpose. This method was first employed by *Kottmann,* who used digalen for this purpose, but, since its recommendation by *Fränkel* and *Schwartz,* strophanthin in dosage of 0.5–1.0

* [Inasmuch as both clinical experience and such laboratory investigations as those of *Hatcher* have clearly demonstrated that the nausea and vomiting produced by digitalis is usually the result of its action on the vomiting centres, and as the desired effects on the circulation often manifest themselves only with doses which also produce these undesirable effects, one must accept with extreme caution the claims made for any preparation of digitalis or any of its group that it does not cause gastric disturbances. Ordinarily this is equivalent to stating that the preparation is more or less inert in other particulars. The claimed superiority of digipuratum in this respect may appear to be justified by clinical observation, but the translator has seen it cause typical digitalis vomiting. If this drug is really less likely to upset the stomach when given in therapeutic doses, it is perhaps due to the convenience with which sufficient amounts may be given without causing the patient to swallow nauseous tasting mixtures or draughts.—Tr.]

mg. has proved an important advance in therapeutics.* [*Cushny* and *Dock* over ten years ago injected a dilute solution of digitalis into the vein of a human patient, with temporary good results.—Personal communication to translator.]

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TREATMENT OF CARDIAC AND VASCULAR DEPRESSION

By cardiac weakness is understood a disturbance of the circulation which is characterized by weak, rapid, and often irregular pulse, pallor, and sometimes cyanosis. Such conditions may develop in the final stages of many kinds of poisoning as well as in the course of various infectious diseases. In an earlier section (p. 290) it has been stated that cardiac insufficiency, which is equally pronounced in both right and left hearts, results only in a slowing up of the blood flow without the occurrence of stasis. This would typify the conditions in a case of uncomplicated depression, but, as a matter of fact, except as a result of hemorrhage, cardiac weakness is never observed except in combination with a more or less general vasoparesis, for not only the toxins of infectious diseases, but also other cardiac depressants, such as chloral hydrate, chloroform, arsenic, etc., affect both the heart and the vasomotor centres [or the vessels themselves.—Tr.].

* [It should be emphasized that strophanthin and ouabein are both enormously toxic substances. Since their introduction as drugs to be administered intravenously, clinicians have learned that their administration is not unattended with danger. 0.3 mg. is ordinarily a sufficient initial dose and, in the translator's opinion, 0.5 mg. is the largest amount that should be given as a first dose. Further, all those who have used these drugs at all extensively insist on the extreme danger of giving them to patients who have recently taken any considerable amounts of digitalis or its congeners. Two days or so should be allowed to elapse between the last considerable digitalis dosage given by mouth and the intravenous administration of strophanthin or ouabein.—Tr.]

Consequently, the phenomena resulting from vasomotor depression develop simultaneously with those resulting from cardiac insufficiency, or precede or follow them. Moreover, even if the heart is not directly affected by the toxic agents, vasomotor depression being the primary condition, cardiac weakness develops secondarily, for, as stated in the introductory portion of this chapter, the functions of the heart and of the vessels reciprocally affect each other most markedly.

A vasoparesis in the splanchnic system produces the most severe disturbances of the circulation. Under normal conditions the vessels of the abdominal viscera are maintained in a state of moderate contraction by the constantly acting influence of the vasomotor centres. If this influence be removed, the vessels dilate and become a reservoir of such great capacity that its filling deprives the other vascular systems of most of their blood. At the start the organism compensates for this by the constriction of the vessels in other systems, and pallor, due to contraction of the vessels of the skin and muscles, appears before the general blood-pressure has sunk appreciably. From the teleological point of view, this regulating process appears useful, as thus the blood flow through the heart and nervous system is maintained as long as possible, for when this fails the general blood-pressure must sink so decidedly that the insufficient blood flow in the nervous system causes faintness, while inadequate circulation through the cardiac muscle impairs its functional power.

In man the symptoms of such collapse, due chiefly to vasoparesis, closely resemble those resulting from cardiac weakness. In both conditions the blood-pressure in the aorta falls, the pulse tension is lowered, and the pulse becomes rapid and small. This acceleration is due to the depression of the vagus tone, which, in turn, is a consequence of the lowered blood-pressure. In cardiac failure the pulse becomes feeble and small because the strength of the cardiac contractions is primarily depressed; in vasoparesis the same changes occur because the heart contracts when insufficiently filled with blood. In *primary cardiac depression* the heart pumps insufficiently because of impairment of its power to contract, but in *vascular paresis,* even though the cardiac muscle is capable of vigorous contractions, so little blood is received by the heart that only insufficient amounts may be pumped out into the aorta. In each case the effect on the flow of blood throughout the body is the same. It is therefore clear that cardiac weakness and vascular depression may not readily be differentiated by their symptoms and that they usually exist coincidently.

Theoretically they differ from each other in that in conditions of vasoparesis the great veins of the systemic circulation are insufficiently filled, while in primary cardiac failure the blood accumulates largely in the veins of both the systemic and pulmonary circulations. It has, however, been stated previously that cardiac weakness accompanied by a slowing up of the blood flow causes merely an alteration in the blood distribution throughout the body and is very different from those forms of cardiac insufficiency for which stasis is characteristic. If in cases with disturbance of cardiac function stasis is not markedly

developed, there results merely a diminished flow of blood throughout the whole circulation, a relatively insufficient filling of the arteries, and a fall in aortic blood-pressure, just as is the case in conditions of vascular depression.

Circulatory failure resulting from vasoparesis occurs in the advanced stages of many toxic conditions, the vasomotor centres being often markedly depressed by a number of narcotic poisons while the heart is still beating well and the respiratory centre remains sufficiently excitable to maintain life. Although formerly in such cases of circulatory failure it was the custom to consider them as due to cardiac weakness, *Romberg* and his coworkers have correctly insisted that, in the course of infectious diseases, disturbances of the circulation develop which closely resemble the picture seen in vasomotor paresis. Using pneumococci and diphtheria bacilli, as well as pyocyaneus cultures, they were able to show experimentally that, at any rate during a long period during which the blood-pressure continued to fall, this was chiefly due to a vasoparesis and not to any direct harmful action on the heart (*Romberg, Passler, Bruhns u. Müller, Passler u. Rolly*), and that the same holds true for experimentally induced septic peritonitis (*Romberg u. Heinecke*).

In man also the collapse occurring in such conditions may in most cases be attributed chiefly to the central vasodepressant action of the bacterial toxins. However, *Krehl* claims that usually, when the disease is at its height, the heart, too, has been harmfully affected, and that this is not simply a secondary effect of the vasoparesis but a direct effect resulting from the action of the toxins on the heart itself. It has been proved, especially for experimental diphtheria intoxication, that in the more advanced stages a progressive true cardiac depression is superimposed on the depression of the vasoconstrictor centres (*Rolly, Steyskal*). Other poisons causing depression of the nerve-centres produce the same effects, lessened reflexes, depression of the vasomotor and respiratory centres, all occurring together in such poisoning as that induced by chloral hydrate. In healthy animals the heart is less affected by this drug than are the vital centres in the medulla. The diseased heart, however, is much less resistant, so that in chloral poisoning, if the heart be already diseased, death may result from cessation of the heart's action before the respiration fails completely. It would appear that diphtheria toxin may act similarly (*Gottlieb*).

It was, therefore, of the highest clinical importance to obtain, by closer investigation of cases of circulatory failure, new criteria for determining in the individual case whether the damage done to the heart by the toxins of the infection or the vascular depression caused by them is of greater moment, for the choice of the means used for treating the condition must be made according to the conclusion reached. With these conditions and facts in mind, *Passler,* using infected animals, investigated the effect of various cardiac and vascu-

lar drugs in the final stages of the toxæmia, and *Schwartz* did the same for the earlier stages. It is clear, however, that the interpretation of their experiments is attended by great difficulties, for, in the first place, the pathological conditions on which the drugs acted were not sufficiently understood, and, secondly, most drugs affecting the function of the heart also act on the vessels and vice versa.

In cases in which cardiac insufficiency is the predominant feature,

Digitalis is the first drug to be thought of, but the slow absorption of digitalis makes it self-evident that in acute circulatory failure not much can be expected from its oral administration. The intravenous injection of strophanthin is, however, a feasible procedure from which good results might be expected, as the injections are so promptly followed by the full development of its actions, and, as a matter of fact, it has been found clinically that an increase of the volume of the pulse and a rise in blood-pressure often follow the intravenous injection of 0.5 mg. of strophanthin in the collapse of typhoid and that of other conditions. [*Crile's* experiments with the intravenous injection of digitalis in animals suffering from shock would indicate that in collapse of this type strophanthin would be of no value, or would act harmfully.—Tr.]

Camphor may also improve the action of the failing heart. It is used for this indication in doses of 0.1–0.5 gm. dissolved in oil, or in oil and ether, or in ether and alcohol; but, on account of its insolubility, it is but slowly and uncertainly absorbed from the stomach. By reason of its volatility and its solubility in the lipoids of the tissues, amounts sufficient to produce effects on the circulation are quite readily absorbed from the subcutaneous tissues [see p. 316—Tr.], but its action is rather evanescent, for in the body it is transformed into camphor-glycuronic acid (*Schmeideberg*).

Other Actions.—In connection with the general systemic action of camphor the stimulant action on the cerebral function should again be mentioned (p. 24). In animals large doses cause clonic convulsions, but these have been very rarely observed in man, as the margin between therapeutic and toxic doses is so great. The respiratory and vasomotor centres are stimulated, and increased blood flow in the skin causes, even after small doses, a subjective feeling of warmth. Very large doses produce an antipyretic effect in fever. [Its local carminative action on the stomach, with the usual reflex effect, should also be mentioned. Moderate antiseptic powers are also possessed by this drug.—Tr.]

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In conditions of uncomplicated vascular depression no benefit can be expected from the administration of cardiac stimulants, for such can result only if the tone of the splanchnic vessels be restored. If this be done, the previously insufficient blood flow through the vessels of the skin, muscles, and brain becomes sufficient (*v. Basch, Biedl*), and, the heart again receiving sufficient amounts of blood, the pressure in the aorta rises. It is thus that sensory reflexes and centrally acting vasomotor stimulants—for example, strychnine and caffeine—may favorably influence vascular paresis. On the other hand, peripherally acting vasoconstricting drugs, such as epinephrin, may similarly alter the general distribution of the blood in spite of the existing depression of the vasomotor centres.

Sensory Stimuli.—As a general rule, it may be stated that a very strong sensory stimulation reflexly lowers the blood-pressure, while weaker stimuli raise it. The effects resulting from the use of mustard plasters and baths or of friction with skin irritants, etc., are best explained as resulting from such reflex actions. By the use of the plethysmograph it may be shown that the kidney volume diminishes while the blood-vessels are more completely filled and the blood-pressure rises under the influence of such sensory stimulation (*Wertheimer, Roy*).

Strychnine is the best example of a central vasomotor stimulant, its action on the circulation being a partial expression of its action on the central nervous system. Therapeutically it is of importance that the action on the vasomotor centres develops before the occurrence of the convulsive symptoms. In this stage mild sensory stimuli, such as blowing on the skin, reflexly cause a rise in blood-pressure in the rabbit. However, a persistent rise in the blood-pressure occurs in normal animals only when the increased reflex excitability of the motor centres of the cord is fairly evident (*Denis*). With depressed excitability of the central nervous system, the danger of causing convulsions is much lessened, and it has been shown that strychnine may improve the circulation in chloralized animals without necessarily causing convulsions. These actions are the basis for the administration of this drug in acute alcohol or chloral poisoning, as also in other conditions with similar disturbances of the circulation, a practice much more common in other countries than in Germany.* In England and America a direct favorable action on the tone of the heart muscle is attributed to strychnine, and recent experiments of *Cameron* indicate that this is the case.

* [Many careful clinicians as a result of painstaking investigation of the effects of strychnine under such conditions have lost their faith in this drug as a means of improving the circulation in infectious disease.—Tr.]

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Caffeine.—The less dangerous caffeine resembles strychnine in its action on the circulation, but never increases the blood-pressure to so great an extent. In previous sections it has been shown that caffeine also is a stimulant for the whole central nervous system (p. 25ff), its vasomotor actions going hand in hand with the stimulation of the respiratory centre and of the cerebral function. In this way is explained the fact that caffeine is one of the most useful analeptics in cases where the circulatory failure results from depression of all the functions of the central nervous system.

Experimentally it has been shown that the vasomotor excitability in dogs poisoned by alcohol is increased under the influence of caffeine and that the blood-pressure returns to a normal height after moderate doses (*Binz*). This return of reflex excitability may also be well observed in chloralized rabbits, *Pässler* studied the actions of caffeine on the depressed circulation of infected rabbits, and found that subcutaneous injections of caffeine-sodium salicylate raised the lowered blood-pressure even in the final stages of pronounced vasomotor depression. Under these conditions the reflex excitability of the vasomotor centres was restored or improved, and this favorable action persisted for a considerable time—up to 1½ hours.

In experiments on animals it may be shown that it is especially moderate doses of caffeine which favorably influence the blood-pressure, an increase of the dose causing further rise, and very large doses or rapid intravenous injection being followed by a fall. This is due to the depression of the functional power of the heart which undoubtedly occurs after toxic doses of caffeine. The discussion of the cardiac action of caffeine (see pp. 267–8) has made it evident that under normal conditions it produces no favorable effects on the performance of the heart, and that after large doses there is a diminution of the amount of blood expelled by the heart in the unit of time. This should soon result in a fall of the arterial pressure, but actually this remains high, as a result of the opposing influence of the vasoconstriction caused by the drug (*Bock*). Thus, during the action of caffeine we must assume that increased tone of the splanchnic vessels occurs simultaneously with lessening of the heart's pumping capacity.

Further, as has been previously mentioned, caffeine exerts two actions, each of which tends to affect the frequency of the pulse in opposite directions. On the one hand, it stimulates the vagus centre and slows the pulse (*Wagner, Swirski, Bock*), and this effect appears to be the predominant one resulting from therapeutic doses in man (*Riegel*) [? Tr.]. Following larger doses, on the other hand, the

pulse is always accelerated, as a result of stimulation of the accelerator terminations in the heart. It is possible that this action on the motor centres in the heart plays a more important rôle in pathological conditions.* From what has been said, an increase in the blood-pressure following the administration of caffeine is to be attributed to the vasoconstriction in the splanchnic system as well as to an increased frequency of the pulse in the later stages of its action.

Therapeutically this power of bringing about an alteration in the distribution of the blood is made use of in conditions of vascular depression. It is possible, too, that this forcing of the blood out of the visceral vessels, as well as direct stimulation of the cerebral function, accounts for the use of the various beverages containing caffeine. The effect of caffeine in overcoming the feeling of fatigue after eating may be due to the action of caffeine in preventing the hyperæmia of the intestinal vessels which usually follows the ingestion of large amounts of food, and thus preventing the relative anæmia of the brain which accompanies hyperæmia of the portal system. The increased blood supply to the skin expresses itself as a subjective feeling of warmth following the drinking of beverages containing caffeine.

The indirect effect on the heart resulting from the rise in blood-pressure due to central vasoconstrictor stimulation is of much importance, for under the influence of caffeine the constriction of the visceral vessels brings larger amounts of blood to the right heart, and as a result an improvement of the cardiac function occurs. This is quite different from the effects in the heart-lung circulation (*Bock, Hering*), where the systemic vessels have been eliminated and therefore can exert no influence on the circulation. [This favorable effect on the cardiac function is still further augmented by the peripherally induced dilatation of the coronary vessels.—Tr.] Santesson has in indisputable fashion experimentally demonstrated an indirect improvement of the cardiac function due to this factor. It is probable that in pathological conditions the increase of the absolute power of the heart,—*i.e.*, its ability to overcome a greater resistance—is of importance. A weaker heart could thus better meet the demands which an increase of the blood-pressure makes upon its contractile energy.

The soluble double salts, caffeine-sodium benzoate and caffeine-sodium salicylate, are used as circulatory stimulants in preference to the pure caffeine, and are advantageously administered subcutaneously in doses of 0.2–0.5 gm., a dosage about twice as large as that of pure caffeine. Strong black coffee is also much used in conditions of collapse, in narcotic poisoning, and in cases of threatening cardiac weakness, etc.

* [In this connection the reader is reminded of caffeine's power of causing or augmenting extrasystoles (p. 268).—Tr.]

Pure caffeine (or theine) occurs as silky shining needles of somewhat bitter taste. It is soluble in water in the proportion of 1: 50, much more soluble in hot water and in alcohol. It is soluble in 6 parts of chloroform, by the use of which solvent it may be extracted from the crude drugs. Its chemical composition is that of a trimethylxanthine. Theobromine and theophyllin, which are dimethylxanthines, pharmacologically closely resembling it, are discussed elsewhere (see p. 364).

In all parts of the earth, plants in which these substances occur are used for beverages or as stimulants. A cup of coffee prepared from 16 grammes of roasted beans contains about 0.1–0.12 gm. of caffeine. The same amount, with some theophyllin, is contained in an infusion made from 5–6 gm. of dried tea leaves. Kola nuts (Kola acuminata) come from Africa, while cocoa, which contains theobromine, Paraguay tea (Ilex paraguayensis), and guarana paste (Paullinia sorbilis), which contains especially large amounts of caffeine and which has been much used for the relief of headaches, all come from America.

Other Constituents of Tea and Coffee.—Besides caffeine, by all means the most important factor in producing their effects, the different beverages and stimulants of this group contain other substances which also contribute to their general effects. In coffee, substances with aromatic odor, formed during the roasting from legumin, sugar, and resins, and in tea, ethereal oils contained in the leaves, are of some physiological significance. These beverages owe their characteristic odor and taste to the presence of these substances, which also exert some action on the central nervous system, causing an increase in the frequency of respirations, muscular restlessness, and distinct psychic stimulation. The so-called caffeine-free coffee, from which about two-thirds of the caffeine has been removed by extraction with benzol, preserves its pleasant flavor while the stimulating effects on the nervous system are largely lacking (*Harnack*).

Other Actions.—In connection with the general picture of the caffeine action the reader is referred to the action on the cerebral function (p. 25 ff.), on the respiration (p. 335), on the renal function (p. 360 ff.), and on that of the muscles. Its effects on the body temperature are of some interest, after moderately large doses the temperature sometimes rising 0.5° C. and after toxic doses more than 1° C.

Acute poisoning by caffeine has been observed by investigators who intentionally poisoned themselves and after immoderate drinking of beverages containing caffeine. Conditions of tipsy excitement, sleeplessness, vertigo, and muscular tremors, as well as nausea and diarrhœa, or pronounced frequency of micturition, may result from injection of 0.5–0.6 gm. After injection of larger doses of about 1.0 gm., in addition to these symptoms, palpitation and irregularity of the heart,* and marked increase of the pulse frequency, with a feeling of anxiety and at times some of the symptoms of angina pectoris, may arise (*Lehmann, Curschmann*). Usually the poisoning passes off gradually without any serious after effects. As much as 1.5 gm. has been taken by rather insusceptible individuals without serious results (*v. Frerichs*).

* [Due to extrasystoles.—Tr.]

Only a small part of the caffeine administered is excreted unchanged in the urine (*Rost*); another portion appears in the urine, after a gradual splitting off of the methyl radicals, as monomethylxanthine and xanthine, but the largest portion is entirely decomposed in the body. The dimethylxanthines suffer a similar loss of their methyl radicals (*Bondzynski, Albanese, Krüger*).

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Camphor is another drug used for its effects on the arteries. On page 274 it has been stated that this drug brings about changes in the distribution of the blood and in the blood-pressure by stimulation of the vasomotor centres, but these effects are obtained in normal animals only by the administration of doses large enough to cause convulsions. In man, however, the doses usually are much smaller than those which cause convulsions, and yet it is certain that the subcutaneous injection of 0.1–0.4 gm. of camphor frequently improves the circulation, though often only temporarily, even when the patient is *in extremis*. In accordance with this are *Pässler's* observations of the distinct improvement of the vasomotor function which followed the injection of camphor in infected animals((?) Translator's note, p. 316).

This suggests that perhaps camphor produces more marked effects on the functions of these centres when they are depressed than under normal conditions. It has often been observed that when the tone of the centres is diminished they react to smaller doses of stimulating substances than when they are functioning optimally, somewhat as a string may be stretched by less power if its tension has been previously diminished.

Thus far this fact, of equal practical and therapeutic importance, is not thoroughly understood. In a similar fashion the central innervation of muscular movements is distinctly stimulated by alcohol or caffeine if these be administered in conditions of fatigue (*Frey, Joteyko*), although the normal muscle innervation is not measurably influenced by similar doses, and the same is true of the action

of similar doses of alcohol on the respiratory centre (*Wendelstadt*). By such analogy it may, therefore, be possible to explain the fact that certain drugs improve the depressed function of the vasomotor centres, even though the optimal normal function is uninfluenced by equal doses.

In addition, the results of stimulation of the vasomotor centres are much more apparent in pathological conditions of the circulation than in conditions of health, for moderate vasoconstriction causes in the healthy animal only an alteration in the distribution of the blood, and, on account of the normal compensatory regulations, the blood-pressure need not rise. If, on the other hand, in pathological conditions of the circulation this compensatory regulation is disturbed and the portal vessels dilated, these drugs stimulating the vasomotor centres cause constriction of the abdominal vessels and bring about a normal distribution of the blood once more, and thus the previously lowered blood-pressure is raised.

[*Heard* (Am. Jour. of Med. Sci., 1913, vol. 135, p. 238) has recently observed a number of patients suffering from various diseases, to whom camphor was administered hypodermatically. He reports that doses ranging from small doses of a few grains up to as much as fifty grains, produced no definite effects on the circulation. They also failed to favorably influence auricular fibrillation.—Tr.]

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Alcohol.—It is proper to consider from this point of view the often repeated experience of the favorable effects of small doses of alcohol in circulatory failure. *Kunkel* states that "the unprejudiced observation of physicians permits no other conclusion than that alcohol, at least in certain pathological conditions, exerts a favorable influence on the depressed cardiac and respiratory functions. A few spoonfuls of a good wine administered to a patient in profound collapse, with scarcely perceptible pulse and hardly perceptible respiration, and pallid cold face, often, after a few minutes, cause color to reappear in the cheeks, as the pulse becomes fuller and the respirations deeper and more regular." On the other hand, there are many who deny these favorable effects. The stimulation of the respiratory centre, especially in conditions of fatigue, has been experimentally proved (see p. 47). If, as seems to be the case, alcohol under certain conditions favorably influences the circulation, this, according to our present knowledge, is to be attributed in part to its action on the heart, and in part to its vasomotor actions. On page 259 it has been stated that recent experimental investigations have demonstrated that alcohol may bring about an improvement of the circulation, especially if the heart action be enfeebled.

The cutaneous vessels dilate even after small doses of alcohol, as a result of the diminution of their tone, but at the same time the pressure in the aorta rises somewhat. This alone renders it probable that other vascular systems must be contracted during the action of the alcohol, and, in fact, alcohol appears to constrict the visceral vessels, *Dixon,* by the use of the plethysmograph, having recently shown that the constriction of the intestinal vessels occurs coincidently with the rise in blood-pressure. According to this author, the splanchnic vasoconstriction is in part the result of an action on the centres, and it is this portion of the pharmacological action of alcohol which may perhaps be of value in conditions of circulatory failure. However, it is certain that the vasoconstriction is in part due to peripheral actions, for it occurs even after the elimination of the vasomotor centres (*Kochmann, Wood* and *Hoyt*).

In this way alcohol alters the distribution of the blood by forcing it from the abdominal viscera and at the same time by dilating the peripheral vessels. As a result of the preponderance of the vasoconstriction, there is an improvement of the circulation, especially if the blood-pressure were previously abnormally low, and in this way the blood flow through the heart is indirectly improved. In man, too, it is possible to demonstrate a rise in blood-pressure after small doses of 60–80 c.c. of 10 per cent. alcohol or wine (*Binz*).

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Ether.—Next to camphor, ether is the drug most often used as an analeptic in conditions of failing circulation. The reflexes due to the sensory irritation at the place of application were formerly considered to be alone responsible for the favorable effect on the circulation which followed its subcutaneous injection or its internal administration (Hoffmann's anodyne in fainting). Recently *Derouaux,* using plethysmographic methods, found that small doses of ether, just as is the case with alcohol, carried by the blood to the internal organs caused a vasoconstriction, so that under some circumstances the blood-pressure may rise considerably. This is especially the case if the blood-pressure was previously abnormally low. On the other hand, it has not been possible to demonstrate that ether exerts a favorable action on the isolated heart, although, according to *Derouaux,* the heart beating in the intact circulation beats more powerfully and rapidly while the blood-pressure is raised. This effect on the heart is, therefore, to be considered as the result of the

better blood flow through the coronary vessels. The analeptic effects of ether, which have always been claimed by physicians, should, accordingly, be attributed to the improvement of the distribution of the blood resulting from stimulation of the vasomotor centres [and in addition to the local constricting effect on the splanchnic vessels.—Tr.] as well as to its stimulant action on the respiratory centre.

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Saline Infusions.—It is possible in still another fashion to help a circulation which is failing as a result of vasoparesis. By increasing the volume of blood it is possible, for a time, to obtain the desired better supply of blood to the nervous system and to the heart. An internal hemorrhage, as it were, results from the relaxation of the splanchnic vessels, the total cross-section of the vascular tree thus becoming too large for the amount of blood present in the body. In such case the necessary rapidity of blood flow through the vital organs may be secured by a better filling of the vascular systems as well as by a constriction of the dilated vessels. In place of the dangerous transfusion of blood (often resulting in hæmoglobinuria, damage to the kidneys, etc.), subcutaneous or intravenous infusion of indifferent isotonic salt solutions may be employed for this purpose. Of these the alkaline Ringer's solution which contains calcium is the best. [Direct arm to arm transfusion, especially advocated by *Crile*, has many advantages, but for obvious reasons it is not always available.—Tr.]

If the vascular tone be normal, such an artificial increase in the contents of the vessels will be removed from the circulation extremely rapidly, as was shown long ago by the experiments of *Cohnheim* and *Lichtheim*. If, however, the blood-pressure be low, the salt solution passes from the vessels into the tissues and the urine much more slowly and remains in the blood for a considerable period. When the splanchnic innervation is functioning normally, the splanchnic vessels are able to take up considerable excess of fluid, and, therefore, under normal conditions the blood-pressure is not markedly raised by saline infusions, even during the period in which the solutions introduced have not yet been removed from the blood. If, on the other hand, the splanchnic system is already overfilled as a result of vasomotor depression, its capacity for absorbing more fluid is lessened, and thus the introduction of even moderate amounts of fluid markedly raises the blood-pressure and thus brings about an improvement of the depressed circulation (*Pässler*).

In such fashion saline infusions may act favorably in the depressed circulation of infectious diseases, and also by "washing out" various toxins and other poisonous substances (*Dastre, Sahli, Bosc, Lenhartz*) so far as these are not firmly combined with the tissues,—

for example, diphtheria toxin (*Enriques*). In case the body has lost large amounts of water, as in cholera and cholera morbus, infusions also counteract the dehydration of the tissues. It is to be remembered, however, that saline infusions can be of permanent value only indirectly (by favoring the excretion of poisonous substances, etc.), for the vasomotor centres remain depressed, notwithstanding the better filling of the vascular system, so that, in spite of the fact that the blood-pressure is raised by the infusion, if the experimental infection be a grave one, sensory stimuli remain ineffective so long as the toxines causing the vascular paresis continue to be produced (*Pässler*).

The conditions are much more favorable for the life-saving action of infusions in cases where death is threatened from hemorrhage. *Goltz* was the first to assert that death after extensive hemorrhage at times occurred not because the amount of blood remaining was insufficient to maintain the internal respiration of the tissues, but because it was not sufficient to maintain the circulation. In true hemorrhage, just as in the so-called "bleeding" into the splanchnic system, the first endeavor of the organism is to supply sufficient blood to the vital organs by compensatorily constricting the vessels of the skin and muscles. If this regulatory mechanism and the inflow of fluid from the tissues into the blood are not sufficient to bring about a sufficient flow of blood into the heart, cardiac weakness results just as in the case of paralysis of the vessels.

Hardly any other symptomatic therapeutic effects may be better demonstrated than the reviving effect of saline infusion after an animal has been bled until respiration ceases and the pulse disappears.

The experimental proof that saline infusions may save life after otherwise fatal hemorrhage was first attempted in experiments on dogs. Here, however, it was found to be difficult to estimate the amount of blood in the individual animals, for this varies within considerable limits. Loss of blood in amounts less than 4.6 per cent. of the body weight are, as a rule, well borne, even without infusion, while if the blood loss exceeds 5.1–5.4 per cent., death usually ensues. However, the majority of the more recent observers are of the opinion that when hemorrhage reaches this amount infusions are no longer able to preserve life permanently, but that in spite of temporary success the dogs die later as a result of the loss of hæmoglobin (*Maydl, Schramm, Feis*). However, there is no doubt that infusions regularly bring about rapid recovery in our experimental animals after hemorrhage, even if before the infusion the respiration has ceased, the reflex excitability has disappeared, and the heart beats have become unrecognizable (*Kronecker*).

According to all clinical experience, it appears that in man infusions have a greater life-saving power than in our laboratory animals (*Schwarz, Schönborn, Küttner, Laufer*). This difference between clinical experience and the results obtained from animal experimentation is probably due to the fact that the human vascular system, especially after severe operations (chloroform narcosis), is not capable of adapting itself to large blood losses to so great a degree as is the vascular system of our laboratory animals. As a result, exsanguinated men are much more likely to die from the mechanical

results of hemorrhage than are the latter (*Leichtenstern*). In the dog, for example, on account of the completeness with which the regulatory constriction of the splanchnic system compensates for hemorrhage, cessation of the respiration and disappearance of the pulse occur only when the bleeding is so great that it necessarily will result fatally on account of the loss of the red cells, while in man collapse appears to develop after much less severe hemorrhage. For the significance of transfusion in replacing blood-cells lost by hemorrhage or otherwise rendered useless, see page 435.

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Epinephrin.—The most efficient means for the rapid restoration of the circulation in all conditions of vascular depression is the intravenous injection of epinephrin. This aids the halting circulation in another way than do the above discussed vasomotor drugs, for it constricts the arterial path by acting locally on the vessel walls (p. 279), and is able to restore the tone of the splanchnic vessels even after they have been completely relaxed as a result of vasoparesis of central origin. In this way, in spite of the persisting paralysis of the vasomotor centres, the abnormal distribution of the blood is changed back to the normal so long as the epinephrin action lasts, for central stimulation of the vessels is replaced for the time being by an increased peripheral stimulation. As this drug is at the same time a powerful stimulant for the heart's action, it would be the ideal drug for combating circulatory failure if its action were not so fleeting. However, its good effects appear to last especially long when it is used in cases of circulatory failure.

The revival by epinephrin of hearts poisoned by chloroform and potassium was demonstrated experimentally a good while ago (*Gottlieb*). More recently it has been shown that animals dying as a result of poisoning by diphtheria toxin, with a blood-pressure as low as 30–40 mm. Hg, may be kept alive for as long as 7 hours if this drug be administered intravenously, the blood-pressure remaining at

a normal height for as long as 30–40 minutes after a single injection (*Fr. Meyer*). The respiration improves and the reflexes return, while the weak and very slow pulse becomes strong and rapid. The drug's actions on both the heart and the vessels appear to be involved in this astonishingly successful experimental therapy. In consequence of the narrowing of the blood path, the rapidity of the blood flow is increased and the heart receives again the normal quantities of blood, while the ability of the heart to do this, in spite of the extensive damage done to it by the diphtheria toxin, is doubtless due to the direct action of the epinephrin in causing a strengthening of the contractions and an increase in their rate.

In all cases of central vascular depression (*e.g.*, poisoning by chloral hydrate, by depressing diphtheria toxins, etc.) or of peripheral paralysis of the splanchnic system (*e.g.*, acute arsenic poisoning), in experiments on animals, epinephrin will bring the blood-pressure back again to the normal, although it may previously have fallen nearly to zero.

Clinically, intravenous injections of epinephrin were first tried by *L. Heidenhain,* who used it in combination with saline infusions in the circulatory failure of severe general peritonitis. [*Crile,* of Cleveland, recommended and used such injections in the treatment of shock and other conditions of collapse considerably earlier than the above-mentioned author.—Tr.] In such conditions (peritonitis) the pathological distribution of the blood results from the inflammatory hyperæmia of the mesenteric and peritoneal vessels, and, according to *Heinecke,* also from a depression of the vasomotor centres by bacterial toxins. According to *Heidenhain's* frequently corroborated experiences, this "internal hemorrhage" due to vascular depression may often be combated with striking success by the slow injection of about ½ mg. of epinephrin in ¾–1 litre of physiological saline solution heated to the temperature of the body. In cases in which the patient is still able to overcome the infection, this procedure may be a life-saving one.

Kothe's recommendation to add epinephrin to the fluid infused in cases of threatening death from hemorrhage is quite as rational, for thus not only are the vessels better filled, but in addition their tone is improved. In accordance with the facts first observed experimentally, such experience of its use in man, as is at present available, has shown that these intravenous injections exert a powerful reviving influence in every form of collapse of the circulation. Thus, *Kothe* by intravenous injection of ½–1 mg. of epinephrin was able to revive patients who, following spinal anæsthesia, were moribund, without perceptible heart beat and with abolished corneal reflexes and interrupted respiration, as well as cases of severe post-operative shock. The heart action improved immediately, and after a few seconds the pulse could again be felt, and the respiration and other functions of

the nervous system gradually returned to normal. Recently, *John* has reported favorable results from this procedure in most severe circulatory collapse in the course of pneumonia, septicæmia, etc. Even when all other analeptics (strophanthin intravenously injected, caffeine, camphor, etc.) had failed, the threatening cardiac weakness was at once relieved by ½–1 mg. of epinephrin, and often permanent life-saving results were obtained.

In all such cases in which epinephrin is injected, the immediate strengthening of even a most alarmingly weakened heart action indicates that the direct action on the heart coöperates with the vasoconstricting action, and this improvement of the circulation then brings about an improvement in the vitally important functions of the central nervous system. The extent to which such results may succeed in preserving life depends on whether the cause of the circulatory failure—for example, the vascular depression—still persists or whether, as in shock or chloroform poisoning, the circulation needs support for only a short critical period. No good can result from increasing the size of the dose injected at one time, but, on the contrary, too large doses, by causing too great a rise in the blood-pressure, are dangerous to a heart already overtaxed to its limit of endurance.* On the other hand, repeated injection of small doses is well borne. When one considers how fleeting is the effect of epinephrin in experiments on animals, the long duration of the effect produced by a single injection in man under these pathological conditions is very striking, the improvement in the circulation lasting sometimes 6–8 hours and longer. It is probable that this is the result of the favorable effect on the vasomotor centres, they receiving for a time sufficient amounts of blood which thus favor their restoration to more normal function.

Very recently the subcutaneous injection of epinephrin has been tried in the treatment of circulatory failure, large doses (up to 6–10 mg.) being given. [The translator has seen the subcutaneous injection of 1 to 1.5 mg. followed by a very alarming rise in the blood-pressure and a whole clinical picture resembling closely the results of intravenous administration of large doses to animals. He, therefore, believes it proper to warn against the subcutaneous injection of large amounts.—Tr.]. However, this method of administration seems less rational than intravenous administration, inasmuch as epinephrin, by its local vasoconstricting action, prevents its rapid absorption, and therefore must remain inactive in the subcutaneous tissues. [Although, *a priori*, this would be expected, it has been indisputably shown that in man subcutaneous injections of epinephrin produce very distinct effects, and many clinical observations would indicate that its subcutaneous injection is frequently followed by more or less lasting improvement of the circulation.—Tr.]

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* [In the laboratory such large doses appear at times to cause fibrillation of the ventricle. Consequently care should be taken not to give too large doses.—Tr.]

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Digitalis Group.—A lasting improvement in the distribution of the blood might be expected to result from the constriction of the intestinal vessels which follows the administration of the members of the digitalis group. Experimentally it is possible by their use to raise the blood-pressure of infected animals—for example, in diphtheria (*Pässler, Meyer*)—and it is not impossible that the successful results of the intravenous injection of strophanthin in conditions of collapse of the circulation are at least partly due to the vasoconstriction which this drug induces (see p. 306).*

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TREATMENT OF VASCULAR CRISES AND VASOCONSTRICTION

Without doubt tonic vasoconstriction plays an important, but as yet insufficiently understood, rôle in pathology. General contraction of the vessels and vasoconstriction in special regions must be separately considered. Of the general vasoconstrictions only those due to toxic agents are at all well understood. They may result from a stimulation of all the vasomotor centres, as, for example, in asphyxia or in strychnine poisoning, or they may be due to a more or less general, peripherally caused vasoconstriction such as that following the intravenous injection of epinephrin.

Both types also occur as endogenous pathological phenomena. Thus, the accumulation of carbonic acid in the blood, which results from insufficient arterialization, causes an over-excitability of the vasomotor centres, and this is probably the chief cause of the rise in blood-pressure observed in conditions of stasis [in combination with the increase of viscosity due to the excess of carbon dioxide.—Tr.]. A general increase in the peripheral vascular tone may, on the other hand, be due to a too free secretion of epinephrin in cases in which the inner secretion of the adrenal glands is pathologically disturbed. [This has been asserted to be the cause of the commonly observed hypertension of Bright's disease, but this view has also been strenuously combated. At present we are not in a position to state the cause of this hypertension, but can simply attribute it to an increased general vascular tone.—Tr.] Finally, the vasomotor centres are susceptible to manifold reflex influences and thus may be pathologically influenced by various distant organs.

* *Crile's* observations on dogs in shock indicate that members of the digitalis group are not helpful, but, on the contrary, are actually harmful in shock.

A general increase of the vascular tonus has, as its first result, an alteration of the distribution of the blood, for all vascular systems are not equally constricted, the vessels in the splanchnic system being more affected than the others. The vessels of the skin and muscles by active dilatation serve a regulating purpose, while other vascular systems, such as that of the brain and that of the lungs, in a more passive fashion adapt themselves to take up the blood squeezed out from the abdominal viscera. Overfilling of the brain with blood may therefore result from an insufficiently compensated vasoconstriction in the splanchnic system, and the insomnia of many individuals in high altitudes may be due to such moderate disturbances, for a high altitude causes an increase in the general vascular tone. Such disturbances in this compensatory regulation occur particularly in arteriosclerosis, *Romberg* and *O. Müller* having shown that the vessels in the extremities react with increasing lack of promptness to the reflex action of heat and cold as the arteriosclerosis progresses. Vascular crises, therefore, are not so readily compensated for in arteriosclerotic patients as in normal individuals.

Marked constriction of the splanchnic vessels—for example, that occurring in strychnine poisoning or in asphyxia—produces secondary effects on the heart, if the blood does not find sufficient accommodation in other regions, the pressure in the aorta rising and the blood accumulating in the heart and in the pulmonary circulation (*Waller*). For these reasons it is clear that extensive vasoconstriction may cause a diminution of the pulse volume of the left heart,—*i.e.*, a relative or absolute insufficiency of the heart,—and under these conditions vasodilating agents may indirectly improve the cardiac function.

Local vasoconstriction in different parts of the body is much more common than general vasoconstriction. The cutaneous, cerebral, coronary, and intestinal vessels are especially likely to be thus affected (*Pal*). Spasmodic persistent contractions of the renal vessels may also occur as a result of reflex influences (reflex anuria).

Cold causes a constriction of the cutaneous vessels not only at the place of application but reflexly all over the whole surface of the body. If the vasomotor centres be very excitable, cold may thus be responsible for disturbances of the circulation. In a similar manner the toxins of various infections cause spasmodic contraction of the cutaneous vessels, and chills result. In certain forms of shock the same conditions may be observed, while in other conditions the contraction of the cutaneous vessels may be brought about secondarily,—for example, through diminution of the amount of blood in certain anæmias or as a result of its concentration in the algid stage of cholera.

Cutaneous vascular cramp causes pallor and a feeling of coldness. This type of vasomotor disturbance is especially likely to occur in the extremities, and ranges from that of slightest degree causing cold hands and feet up to the most severe type such as occurs in Raynaud's

disease. These vascular crises in the internal organs cause the so-called vessel pain (*Gefässchmerz*) and attacks of functional disturbance in the organs whose blood supply is thus rendered intermittent (intermittent claudication). Such would appear to be the cause of stenocardial attacks or angina pectoris. The hypothetical explanation of such disturbances, as resulting from vascular cramp, often finds its best corroboration in the curative effect of vasodilating drugs or agents.

In certain forms of migraine it would appear that chronic contraction of the meningeal vessels is more or less responsible for at least a part of the trouble. Other varieties of headache—for example, that in fever and in uræmia—are also attributed to a spastic contraction of the cerebral vessels. It may be that sea-sickness also stands in some causal relationship to such tonic contraction of these vessels [see note, p. 325.—Tr.].

Finally, it would appear that in different conditions of stenocardia and related disorders the causal moment is a suddenly occurring contraction of the coronary vessels (*R. Breuer*). In such cases the vascular crises may occur simultaneously in several regions and may pass from one to another. For example, in angina pectoris the tonic contraction may extend from the cutaneous vessel of the upper extremities to the coronary vessels.

The general blood-pressure is affected by the local vascular crises only when these involve extensive vascular systems, as, for example, in the case of lead colic, where the intestinal vessels are tonically contracted. On account of the extent of the cutaneous vascular system in man, vascular crises limited to the vessels of this system may also affect the aortic blood-pressure. However, in most cases the blood forced out from the constricted system finds a place in other parts—for example, in the vessels of the brain—which dilate when the vessels of other regions are tonically contracted. This would appear to explain the frequently observed coincidental occurrence of "cold feet and hot head."

The regional vascular crises are a result of autochthonously or reflexly caused excitation of the appropriate vasoconstrictor centres, but it appears that changes in the vessel walls, such as are found in arteriosclerosis and chronic nicotine poisoning, dispose to their occurrence. In accordance with these facts, visceral crises may be relieved by drugs (narcotics) diminishing the excitability of the vasomotor centres, and also by those acting peripherally, which diminish the pathologically increased tonus of the vessel walls or render them less susceptible to the influence of the vasomotor centre. Caffeine and theobromine are examples of drugs acting in the latter fashion, while amyl nitrite and the other nitrites, with their central and peripheral vasodilating action, take an intermediate position.

The narcotics of the alcohol-chloroform group are of value as vasodilating drugs in so far as they, like alcohol, are otherwise not very poisonous, or, like chloral hydrate, even in small doses [? —Tr.].

depress the vasomotor centres. They act, it is true, on the vasomotor tone of all the vascular systems, but certain systems—above all, the cutaneous and the cerebral vessels—are especially readily dilated by them. Still more elective is the relaxing effect on the cutaneous vessels exerted by the members of the *antipyrine group,* which will be further discussed in the section on the pharmacology of temperature regulation. These drugs are especially efficient in relieving the tonic contraction of the cutaneous vessels which occurs in chills. These antipyretic and sedative drugs, moreover, influence the circulation of the brain in even smaller doses. As shown by *Wiechowski,* antipyrine and related drugs, in febrile animals, cause, as their first appreciable vasomotor effect, a distinct dilatation of the intracranial vessels, while the narcotics—for example, chloral hydrate—increase the flow of blood through the brain only as one of the effects of a very wide-spread vasodilatation. It may be that the favorable action of chloral hydrate and other hypnotics in sea-sickness * rests on such a dilatation of the cranial vessels (*Binz*).

The vasodilating action of moderately concentrated *alcohol* (brandy or strong wine) produces quick and useful effects when the cutaneous vessels are tonically contracted,—as, for example, in chills or in the faulty reaction which results from a persistent contraction of these vessels following a cold bath. Alcohol may also prove useful in certain cases of angina pectoris (*Sahli*).

It is probable, too, that the favorable effect of alcohol in certain conditions of collapse, in which the circulatory failure is the result of faulty heart function, is to be explained by the rapid lessening of the tension of the vessels which is produced by proper doses. However, it should be remembered, in this connection, that small doses of alcohol dilate the cutaneous vessels, and that, according to more recent experiments (p. 274), they constrict the visceral vessels. It may be, however, that doses, which produce no effect on the blood-pressure in the normal circulation, will depress the tone of vessels tonically contracted.

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Wiechowski: Arch. f. exp. Path. u. Pharm., 1902, vol. 48, p. 376.

* [It would appear fairly certainly established that sea-sickness is the result of the effect produced by the movements in space of the labyrinth of the ear, and that vasomotor phenomena are, as it were, simply the reflexly produced effects of this. If, as appears to be the case, the hypnotic drugs do favorably influence the symptoms of sea-sickness, a more plausible explanation would be that they do so partly by interfering with the reflexes and partly by lessening the unpleasant subjective symptoms of this condition, for both of these effects would result from their general depressing influence on the central nervous system.—Tr.]

The Nitrites.—Amyl nitrite and similar drugs are the most rapid and powerful vasodilating agents which we possess. They are the vasodilators *par excellence.* As may be shown by direct observation, the action of small doses is electively limited to dilatation of the cutaneous vessels of the upper part of the body and those of the brain, while in larger doses, by action on the centres, they relax the vessels throughout the body [with the exception of the pulmonary vessels.—Tr.] In addition, they also act locally on the vessel walls, as shown by their effect on the coronary vessels. *Lauder-Brunton* introduced amyl nitrite into the therapy of angina pectoris in 1867, and in practice this drug has shown itself extremely effective symptomatically in the treatment of this condition.

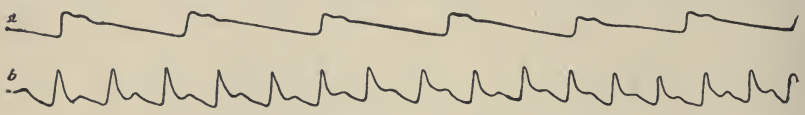
As is well known, the symptom-complex of angina pectoris occurs in heart disease of different types, and consists in sudden attacks of precordial pain associated with a feeling of anxiety and depression, which may be accompanied by more or less marked dyspnœa. Pathologists believe that it is probably caused by a sudden interference with the blood supply of some portion of the heart, for, at the autopsy of such cases, sclerosis of the coronary arteries, causing narrowing at their mouths or in their course, is often found. It may, therefore, be assumed that the chief cause of these attacks is a diminished blood flow in the coronary arteries or their faulty power of accommodation to the need of an increased blood supply to the heart (*Krehl*). If this be so, it is easy to understand the successful results of the administration of a drug possessing such exquisite vasodilating actions.

The most probable supposition concerning the method by which this effect is produced would be that amyl nitrite possesses special powers of dilating the coronary arteries by action on the vasomotor centres controlling these vessels. Unfortunately, our knowledge of their central innervation does not permit us to state that the drug exerts this elective action. On the other hand, *Loeb's* investigations have proved that amyl nitrite may dilate the coronary vessels by a local action on their walls.

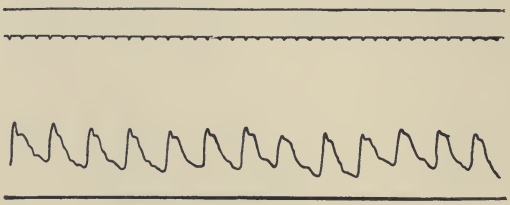
Furthermore, the vasodilatation produced by amyl nitrite may diminish the demands made on the heart in case constriction of vessels in other regions has caused a relative cardiac insufficiency. Thus, the favorable action of amyl nitrite in angina pectoris may be explained quite apart from any direct action on the coronary circulation, for it may be due to the lessening of the resistance against which the heart must work, resulting from the immediate vasodilatation which follows the administration of this drug. In cases of stenocardia the efficiency of other vasodilatating drugs—for example, alcohol—may be explained in a similar fashion. [As it has been shown by *McKenzie* and others that angina pectoris frequently occurs without any evidence of general vasoconstriction and in the

presence of normal blood-pressure, it does not appear probable that the relief which it so often gives in this condition is a result of its general vasodilating action.—Tr.]

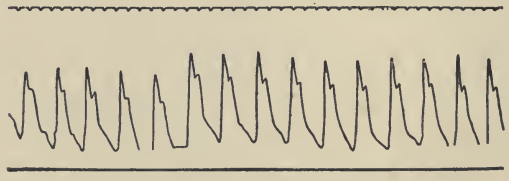
Amyl nitrite does not always entirely or even partially relieve the attacks of angina pectoris, nor should this be expected, for it would appear that this symptom-complex often results from different causes. Consequently, success should be expected to result from its administration only when extensive vasoconstriction is the exciting cause. [? See above.—Tr.] Its efficiency is most readily understood



a. Tense pulse (angina pest). *b*. After amyl nitrite.



Tense pulse before amyl nitrite.



After five drops of amyl nitrite (*Pal*).

Fig. 36.

in those forms of angina described by *Nothnagel* as angina pectoris vasomotoria, in which "pallor and numbness, subjective feeling of cold, and objective decrease in temperature of the skin" would indicate that the tonic contractions of the cutaneous vessels inaugurate the attack.

The effects of the inhalation of a few drops of amyl nitrite appear extremely rapidly, in less than a minute, and often last an extremely short time, but frequently the temporary vasodilatation produced is able to correct the pathological conditions for a considerable period. *Lauder-Brunton* thus describes a case in which he first used amyl

nitrite. "Simultaneously with the flushing of the face the pain disappeared completely, and did not return until the following night. While sometimes the pain returned after about five minutes, renewed inhalation of a few drops caused it to disappear again, and this time for a considerable period." At the same time with the relief of the attack, the cessation of the tonic contraction of the vessels is clearly seen in the radial pulse. This is graphically shown in sphygmograms taken by *Lauder-Brunton*.

Amyl nitrite has also been used in other conditions of disease in which more or less tonic contraction of the vessels—for example, of the cerebral vessels—has been assumed. In this connection, the use of amyl nitrite would appear rational in certain types of migraine in which a striking pallor of the face indicates vascular constriction (hemicrania sympathico-tonica). Quite beyond question is the effect of this drug on the tonic contraction of the splanchnic vessels when it is used in lead colic, the abnormally tense and retarded pulse becoming, at least temporarily, quite normal (Fig. 37) (*Frank, Riegel*).

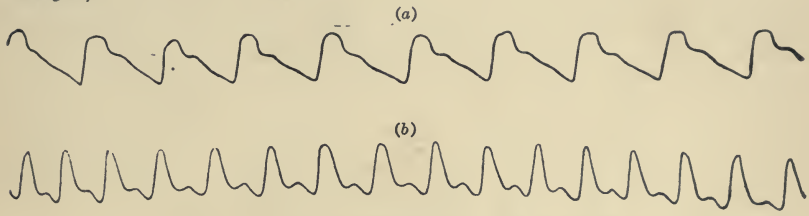


FIG. 37.—*a*, pulse during lead colic; *b*, after amyl nitrite.

The various nitrites act analogously to amyl nitrite, but in general produce more lasting effects. After sodium nitrite (in doses of 0.03–0.06 cg.) the effect is produced in 3–4 minutes, reaches its maximum in 15–30 minutes, and lasts about 1½ hours (*Marshall, M. Hay*).

As a general thing, however, the action of sodium nitrite is considered to be less certain, while larger doses—*e.g.*, 0.5 gm.—produce toxic effects.

The nitric acid esters of the higher alcohols also possess a pronounced nitrite action. Thus, nitroglycerin, in the very small amounts of ½–1 mg., produces in two minutes the same actions on the vessels as the nitrite salts. This similarity in the effects of the nitric acid esters with those of the nitrites is due to the fact that the former are changed in the body into nitrites. Nitroglycerin possesses the advantage over amyl nitrite in that its effects last longer (1½–3 hours) [see above.—TR.]. The same is true of erythrol tetranitrate and other similar compounds. It is stated that sodium nitrate in larger doses acts similarly to the nitrites (*M. Hay*), perhaps because in the body it is partially reduced to a nitrite.

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Caffeine and theobromine and related substances dilate the vessels in certain regions by a peripheral action on the vessel walls. On page 274 it has been stated that caffeine, by its action on the vasomotor centres, produces an opposite (vasoconstricting) effect, which affects especially the visceral vessels that are particularly easily influenced by the vasomotor centres. There is thus an antagonism between its central vasoconstricting action and its direct peripheral vasodilating action, in one group of vessels the peripheral action predominating, and in another the central. As long as the kidney remains under the influence of the vasomotor centres, as a general rule its vessels will be constricted by caffeine [? Tr.], and to a greater or less extent according to the varying individual susceptibility of the vasomotor centres to the action of the drug. On the other hand, caffeine always acts as a vasodilator in a kidney isolated from its nervous connections. With theobromine, which has less action on the centres, the vasodilating action on the renal vessels always preponderates. (See section on diuresis.)

Next to the renal vessels the cerebral arteries are especially affected by the peripheral action of caffeine. *Wiechowski* observed, during the action of caffeine, not only an increased flow through the brain, which he explained as the passive result of the forcing out of the blood from the splanchnic system, but also a direct depression of the tone of the intercranial vessels. The curative action of caffeine in certain types of headache may be due to this action on the cranial circulation.

Finally, experiments of *Hedbom* and *Loeb* indicate that caffeine distinctly dilates the coronary vessels by a peripheral action on the vessel walls, as it does this in the isolated perfused heart. Theobromine acts similarly, and this is probably the explanation of the fact that theobromine preparations have proven so satisfactory in the prophylaxis of anginal attacks [and in other vascular crises.—Tr.]. During the attacks, however, it cannot be used, as its absorption is too slow to relieve promptly the tonic contraction of the vessels. The prophylactic employment of 2.0–2.5 gm. of theobromine-sodium salicylate prevents or moderates these attacks in unmistakable fash-

ion, as has been evidenced by numerous observations made since it was first recommended for this purpose by *Askanazy*. Theobromine and the closely related theocin have also been found useful in the prophylaxis of other conditions dependent on vascular crises. This is probably due to the fact that the depression of the peripheral tonus of the vessels resulting from the action of these drugs renders them less susceptible to the occasionally recurring excitation of the vasomotor centres (*Breuer*).

The alkaloid *yohimbin* (p. 289) also dilates certain vascular systems by a peripheral action. Its nitrate, vasotonin, in probably superfluous combination with very small amounts of urethane, has been recently recommended for subcutaneous injection in the treatment of angina pectoris or other arteriosclerotic disturbances (*Müller u. Fellner, Staehelin*).

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CHAPTER IX

PHARMACOLOGY OF THE RESPIRATION

The respiratory system of mammals consists in the integral portions of the respiratory tract, the larynx, bronchi, and lungs, and in the muscles which control them, these being, in part, the striated laryngeal, intercostal, and diaphragmatic muscles and the unstriped muscles of the bronchi. The respiratory exchange of gases in the pulmonary alveoli depends on the atmospheric pressure, the activity of the motor mechanism of the respiratory muscles, and the elasticity of the pulmonary tissues,—*i.e.,* on the mechanical effects of the respiratory movements, as well as on the resistance which opposes the movement of the air in the air-passages, and the elastic contraction and relaxation of the alveoli.

The frequency, extent, and power of the movements of respiration are directly dependent on the state of excitation of the respiratory centres, situated in the medulla and spinal cord, which are stimulated directly by substances present in the blood and reflexly through centripetal nerves, especially the pulmonary vagus, the trigeminus, and the cutaneous nerves.

Of the factors which influence the excitation of the respiratory centre through the blood, oxygen and carbon dioxide tension are the decisive ones. Abnormally diminished O_2 tension in the blood increases the frequency and depth of the respiration, causing, as a rule, a dyspnœa of a predominatingly inspiratory type, but this occurs only when the O_2 content of the inspired air has sunk to 10 per cent. or less (*Speck, Loewy, v. Terray*). If at the same time the tension of CO_2 is very low, lack of O_2 causes Cheyne-Stokes respiration (*Haldane* and *Douglas*). This is the explanation of the appearance of this phenomenon in high altitudes (*Durig*).

Oxygen. Inhalations.—No appreciable effect on the respiratory apparatus or on the consumption of O_2 and the total metabolism results from an increase of the O_2 contents of the air respired, even when this amounts to 100 per cent. (*Durig, Kraus*). Except in CO poisoning there is no sufficient scientific proof of the value of inhalations of O_2, although these have recently been strongly recommended by clinicians (*McKenzie et al.*).

Most observers, however, report that the inhalation of O_2 exerts a favorable effect on the subjective feelings of patients suffering with dyspnœa and cyanosis,—at any rate, as long as the inhalation is continued. Inasmuch as hæmoglobin cannot absorb more oxygen from a gas mixture rich in O_2 than from the air, this effect cannot be attributed to a greater saturation of the blood-coloring matter with

oxygen. However, the plasma can absorb more oxygen if the oxygen tension of the inspired air is higher than in the ordinary air, and thus it may at times be of some importance to increase the oxygen tension in the inspired air (*Durig*), for plasma saturated with oxygen to an abnormally high degree may raise to the normal the oxygen tension in blood which is unequally, and therefore incompletely, arterialized on account of the existence, here and there in the lungs, of pathological conditions interfering with the gaseous interchange between the blood and the air. It may be that, as a result, the metabolic products which cause dyspnœa are more rapidly oxidized, and that thus the restlessness and the feeling of anxiety due to the dyspnœa may be relieved.

If, as a result of persistent over-saturation of the blood with CO_2 in pulmonary stasis of cardiac origin, or as a result of uræmic poisoning, the respiratory centre has been blunted to the stimulation produced by CO_2, an insufficient oxygen supply frequently, in spite of high CO_2 tension of the blood, causes a condition to develop which is characterized by periodic breathing, the patient falling asleep during the pauses and waking suddenly and anxiously when the respirations start again. In such conditions inhalation of O_2 can often bring about regular breathing once more and thus give marked relief (personal communication, *R. Breuer*). From the above, the symptomatic effects of the inhalation of O_2, especially those obtained as long as the inhalation continues, may be explained (see also *Loewy* and *Zuntz*).

Effects of the Carbon Dioxide Tension of the Blood.—On the other hand, a diminution of the normal CO_2 tension in the alveoli, and consequently also in the tissues, has no stimulating effect on the respiration, while an increase of the CO_2 tension, even a very slight one, markedly stimulates respiration (*Jacquet*). Increased CO_2 tension in the tissues also occurs if the alkalinity of the blood be diminished, a condition which may result from the formation of acid metabolic products during hard muscular work or in fever, diabetes, many poisonings, etc. (*Geppert* and *Zuntz*). In such case the respiration becomes very dyspnœic. It is enlightening that under such conditions the free administration of alkalies may quiet and regulate the respiration.

Effects of Body Temperature.—Without regard to its chemical composition, the temperature of the blood also exerts an influence on the frequency and depth of respiration, increased temperature usually stimulating (*Fick u. Goldstein, v. Mertschinsky, Fridericq, R. H. Kahn*) and lowered temperature depressing it. Therefore, all agents which warm abnormally cooled blood—for example, warm perfusions —or which, like the antipyretics, cool the overheated blood of fever will aid in bringing the frequency of the respirations back toward the normal.

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DIRECT OR CENTRAL RESPIRATORY STIMULANTS

In cases of severe illness or poisoning, deep coma not infrequently develops, the breathing becoming progressively slower and shallower and finally entirely insufficient. In such case the therapeutic indication is to stimulate the respiration,—*i.e.*, to excite the halting mechanism to sufficient activity. This can be accomplished by direct stimulation of the respiratory centre.

The number of substances which directly stimulate this centre is very large. It may be stated that all very volatile poisons stimulate the respiration, and inasmuch as these substances are excreted in the expired air, this stimulation of the respiration is a reaction of the organism readily understood from the teleologic point of view. Hydrogen sulphide, HCN, CO_2, chloroform, ether, alcohol, amyl nitrite, and many others, all act in this fashion, but, for therapeutic purposes, only alcohol and ether are of practical importance in this connection.

Alcohol.—The stimulating effect on the respiration exerted by small amounts of strong wines has long been known clinically; but the question, as to the extent to which this is a reflex effect from the stimulation of the taste and smell or of the sensory nerves of the stomach, or the result of direct stimulation of the respiratory centres, has been responsible for numerous investigations, especially on the part of *Binz* and his pupils.

These authors have been able, in animal experiments, to show that a persistent increase of the ventilation volume—*i.e.*, of the volume of air breathed in and out in the unit of time—resulted from the administration of alcohol irrespective of the manner in which it was administered. This occurred even after intravenous injection, while, when the alcohol was injected toward the centre into the carotid artery, the effect was produced almost instantaneously (*Wilmanns*). From this last-

mentioned observation it is permissible to deduce a direct stimulating action in the central nervous system. Moreover, as alcohol, unlike carbohydrates and fats, cannot be stored up, but is promptly combusted, a part of the persistently increased respiration must be attributed to the larger demand for O_2 and the greater production of CO_2 resulting from the combustion of the alcohol (*Henrijean, Zuntz*). As, however, this action occurs even after the intravenous administration of very small doses, whose combustion can hardly produce such effects, the chief cause of the increased respiration must be sought in a direct central stimulation. According to *Binz,* the ethers present in wines also possess the property of stimulating the respiratory centres.

Ether may be administered internally either pure or mixed with alcohol in Hoffmann's anodyne. Subcutaneous injections of ether are also very efficient, but they must not be administered in the neighborhood of nerve-trunks. [Administered in these varying fashions this drug strongly stimulates the respiration partly reflexly and partly directly.—Tr.]

In addition to the above-mentioned volatile substances, the respiratory centre is stimulated by a number of drugs which increase the excitability of different portions of the central nervous system. In this connection, particular mention should be made of *strychnine, camphor, caffeine, cocaine, atropine,* and other alkaloids of this group, *lobeline, apomorphine,** and the two alkaloids contained in quebracho bark, aspidospermine and quebrachine (*B. Wallace*). For practical purposes, only *camphor, caffeine,* and *atropine* need be considered. [*Strychnine!*—Tr.]

The stimulating action of camphor and the methods of its administration have already been discussed, as also that of caffeine. In this connection it may be mentioned that other substances, which may be obtained by distillation and which increase the frequency of respiration, are contained in tea and coffee (*Heinz, Archangelsky*).

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Atropine.—The central stimulation of respiration by atropine was demonstrated long ago by *Bezold* and has been confirmed by

* Apomorphine stimulates the respiratory centres even after the vomiting centres have been paralyzed in narcosis (*Harnack*). [It later depresses them.—Tr.]

various other observers. It is especially usefully and clearly developed in narcotic poisonings,—for example, in chloral poisoning (*Husemann*) and particularly in morphine poisoning. The following curve (Fig. 38), reproduced from *Vollmer,* shows graphically the results obtained in an investigation of the antagonistic action of morphine and atropine on the respiration.

As large toxic doses of atropine may themselves depress the respiratory centres, the desired success depends evidently on the skilful and careful use of atropine, and this depressing action explains the failures observed in the experiments of various investigators (*Binz*).

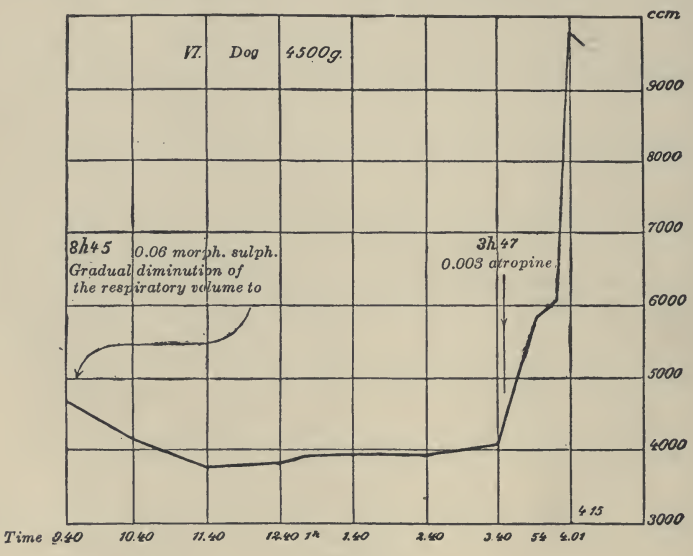

Fig. 38.

Indirect reflex stimulation of the respiratory centre usually produces more marked effect on the respiration than that caused by the use of drugs. Such reflex stimulation may be induced by cutaneous irritation (see p. 341) and by irritation of the nerve-endings of the trigeminal and olfactory nerve in the nose, induced mechanically, as by tickling, or chemically, as by ammonia or vinegar. The widely used smelling salts contain ammonium carbonate with ethereal oils, such as the oil of lavender.

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RESPIRATORY SEDATIVES

The clinical indication is much oftener that of quieting and regulating the respiration than that for stimulation. This is the case where a directly or reflexly induced dyspnœa, spasmodic respiratory movements, or distressing cough demand relief, in which conditions symptomatic relief may be obtained by dulling the sensibility of the respiratory centres.

This property of diminishing the excitability of the respiratory centres is possessed by all so-called narcotics,—*i.e.*, by all substances which depress the excitability of the central nervous system,—but the various narcotics exhibit marked and important differences in this respect. Although all the anæsthetics and hypnotics, belonging to the large "alcohol group," have a sedative action on the respiration, this effect results only from more or less toxic doses, which appreciably

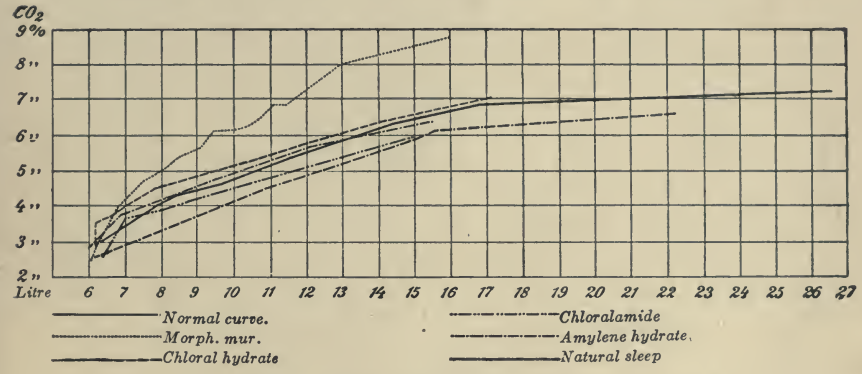

FIG. 39.—Respiratory volume with increasing CO_2 tension of the blood.

or very decidedly blunt the consciousness, the sensibility, and the reflex excitability. They are consequently not suitable drugs for this indication. [The translator most emphatically disagrees with this sweeping statement, for he believes that clinically such drugs as chloral and other commonly used hypnotics may frequently be employed with advantage for this indication and in doses which produce only moderate hypnotic effects.]

MORPHINE

On the other hand, the narcotics of the morphine group depress the excitability of the respiratory centre in a very specific fashion, long before, or without at all, producing other sedative effects.

A. Loewy has introduced, as a very useful means of measuring the excitability of the respiratory centre, the readily graded stimulation which results from mixing different percentages of CO_2 with the inspired air. In man the expired air contains about 3 per cent. of CO_2. If the inspired air be mixed with

increased quantities of CO_2, the CO_2 content of the expired air rises accordingly and may serve as a measure of the effective CO_2 tension in the blood. It has been shown also that as the percentage of CO_2 in the expired air rises from 3 per cent. to about 7 per cent. the respiratory volume increases almost exactly proportionately, and in the same proportion in different individuals and at different times. The curves in Fig. 39, reproduced from *Loewy*, show this clearly. Apparently with higher CO_2 tension a summation effect from different unknown factors develops, for the ventilation volume increases to a greater extent than corresponds to the increase of CO_2 in the expired air.

Neither natural sleep nor that induced by hypnotics, such as chloral hydrate, chloralamide, amylene hydrate, markedly influences the reaction curve, but this is decidedly altered by morphine, even in small doses which otherwise produce no sedative effects. Under its influence the respiratory centre becomes less excitable, so that the CO_2 in the inspired air must be increased much more than under normal conditions in order to cause the usual increase in respiration. The sensibility of the respiratory centre to reflex stimulation—such, for example, as that resulting from stimulation of the sciatic—is diminished in the same fashion as its sensibility to CO_2.

In man, after very small doses of morphine (3–10 mg.) the diminished excitability of the respiratory centre expresses itself by slowed and deepened breathing, for a stronger summation of the stimuli (distention of the lungs and the CO_2 tension in the blood) is needed to excite the rhythmic respiratory movements. This has been proven experimentally by *A. Fränkel*, who observed that the respirations of rabbits under the influence of morphine occurred less frequently but were much deeper.

*Effects of Small Doses of Morphine on the Respiratory Volume of the Rabbit.**

Time, minutes	No. of respirations per min.	C.c. of air respired per min.	C.c. of air in each respiration
1	68	300	4.4
2	64	300	4.6
3	68	300	4.7
5	..	...	...
13	54	300	5.7
26	60	400	6.6
51	52	360	6.9
61	50	440	8.8
71	56	500	8.9

* 0.54 mg. morphine per kilo injected subcutaneously.

Under certain conditions, *morphine may thus increase the ventilation in the lungs beyond the normal,* for during each respiration only a portion of the alveolar air can be replaced by atmospheric air, and this portion, on account of the volume of air contained in the so-called "noxious air-space" of the trachea and bronchi, must be considerably increased by a deep respiration as compared to the amount replaced

during a shallow one. Thus, for example, in the experiments of *Reach* and *Röder* (see also *Loewy*) the alveolar air was found to contain 17 per cent. of O_2 and 2.7 per cent. of carbonic acid when 20 litres of air were respired as a result of 100 respirations to the minute. When the respirations were deeper and slower, the same "minute volume" was respired with only 25 respirations to the minute and the O_2 in the alveolar air was found to be present in the proportions of 19.3 per cent. and carbonic acid in that of 2 per cent. In these figures the greater ventilating effect of deep and slow breathing is clearly apparent.

This effect is increased by the fact that the composition of the air in all parts of the lungs is not the same, for the air is richest in CO_2 and poorest in O_2 in the alveoli lying at the periphery, which expel their contents only during deep breathing and more especially during forced expiration. For this reason forced expirations, such as occur in coughing but especially during sneezing and vomiting, may exert a favorable influence on the renewal of air in the alveoli. Herein may lie a partial explanation of the benefit of the nausea and the retching movements, which the so-called nauseating expectorants induce (*Dreser*).

From such slowed and deepened and, in spite thereof, more efficient respirations, the lungs and the whole respiratory system may experience a beneficial relief, and there may result a saving of strength which may be of greatest importance in enfeebled patients, who have been breathing frequently and ineffectively,—as, for example, cardiac cases or cases with high fever. *By regulating and improving its efficiency, morphine does about the same for the respiration as digitalis does for a diseased and insufficient heart.*

Effects on Cough.—The reflex excitability of the cough centre, which is reflexly stimulated by irritation of the laryngeal and bronchial mucous membranes and perhaps also by reflexes from other organs, is depressed by drugs of the morphine group even earlier and more readily than is that of the respiratory centre proper. This fact has been established clinically beyond all doubt, although experimental proof of it is still lacking, and consequently drugs of the morphine group may be used with good effect in conditions where the indication is to suppress the cough reflex, as in harassing or painful cough, or with the idea of avoiding hæmoptysis, or to relieve laryngeal inflammation or irritation, which is constantly aggravated by coughing.

Morphine Derivatives.—Although these therapeutic effects may be obtained by the use of morphine in proper doses (3–10 mg. for adults, correspondingly smaller doses for children), still its other effects, such as constipation or, in nervously susceptible patients, excitement, as well as the danger of opening the door to the readily acquired habit in chronic sufferers, such as tubercular patients, are ample reasons for

avoiding as long as possible the use of this drug for the relief of cough. This is the more feasible as certain derivatives of morphine do not possess the disadvantages mentioned [in the same degree.—Tr.], while they produce the desirable effects on the respiratory function in even higher degree (*Heinz, Dreser, Fränkel*). Of these derivatives the following are of practical importance:

1. Codeine, a methylmorphine, best administered as codeine phosphate, which is readily soluble in water. It may be used several times daily in doses of 0.04–0.06 gm. for adults (0.1 gm. maximal single dose, 0.3 gm. maximal daily dose). Smaller doses, even when frequently repeated, are of slight efficiency and are not to be recommended (*Fränkel*). Habituation need not be feared, even in case of use for months or years.

2. Dionin, ethylmorphine hydrochloride, in its actions, is very similar to codeine, but it appears to be more powerfully analgesic and constipating, although neither of these actions is as pronounced as with morphine. It may be administered orally or subcutaneously in doses of 0.015–0.03 gm.

3. Peronin, benzoylmorphine hydrochloride, 0.02–0.04 gm. per dose. [Is little used. Resembles dionin.—Tr.]

4. Heroin, diacetylmorphine hydrochloride, which is readily soluble in water, diminishes the excitability of the respiratory centre more strongly than the other morphine derivatives, and even in small doses slows and deepens the respiration. It is in general more like morphine than the other derivatives mentioned, and in children produces a strong narcotic effect (see p. 38). For adults the dose is 3–5 mg., for children over one year ½ mg., under one year ¼ mg. *With this drug there is danger of habit formation.*

Still other substances exert a sedative action on the respiratory centre, as, for example, *camphoric acid*, an otherwise but slightly active oxidation product of camphor. Dose, 1.0–2.0 gm. It may be administered in alcoholic solution (*Heinz* and *Manasse*).

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EMBARRASSMENT OF THE RESPIRATION

Excluding such conditions as compression of the lungs by air or fluid in the pleural cavity and those where the respiratory muscle is mechanically incapacitated,—for example, spasm or paralysis of the diaphragm,—inefficient breathing may be due to a reflex inhibition

of the thoracic movements by pleuritic pain, intercostal neuralgia, etc., to an abnormal condition of the air-passages, or, finally, to a disturbance of the pulmonary circulation. Only these last three causes may be affected by medicinal treatment.

1. **Pain** may interfere with the movements of the thorax on one or both sides. This may be experimentally demonstrated in animals or in man by applying mild irritants, such as mustard plasters or tincture of iodine, to one or both sides. The precordial region appears to be by far the most susceptible portion of the thorax, and particularly so to irritation by mustard plasters (*L. Mayer*). As a result of such irritation the breathing becomes shallower and slower, especially in its inspiratory portion, while the unirritated side compensates with increased movement. Such irritation of the healthy side may be occasionally carried out for therapeutic purposes in order to bring about freer movement of a lung which has become more or less inactive as a result of pleuritic adhesions or other pathological processes.

If the counterirritation be very powerful,—as, for example, that caused by the thermocautery,—the movements of the side where the irritation is applied, although becoming slower, do not become less extensive, but, on the contrary, marked deepening of inspiration occurs, which may last for some time after the active irritation has ceased. Similar favorable effects of slowing and deepening of the respiration may result from milder counterirritation—by tincture of iodine—in case the breathing has been shallow and rapid as a result of spontaneous pain, such as that occurring in pleurodynia, for such mild irritations have some local anæsthetic action. By such means the respirations of the patient may be relieved and improved (see p. 34).

In inflammatory conditions of the mucous membrane of the respiratory tract, drinking or gargling with emollients, such as althea or mucilage of acacia, may give relief by their effects on irritant reflexes.

2. Impairment of the respiration as a result of **obstructions in the respiratory tract** may occur as a result of an inflammation, on account of excessive viscid bronchial secretion, or as a result of spasmodic closure of the air-passages.

Vasoconstricting drugs and those lessening secretions may be used with advantage in inflammatory conditions in the lungs with congestion of the mucous membrane and profuse secretions. The best ones to use are volatile substances such as turpentine and other volatile oils, which may be atomized or inhaled, or, especially in chronic conditions, inhaled in steam. Their deodorizing and antiseptic effects may here be of some value by limiting putrefaction. This is especially the case when true antiseptics, such as balsam of Peru, thymol, creosote, etc., are inhaled. [It has always appeared questionable whether such substances when thus used actually reach the inflamed

structures in amounts large enough to exert any appreciable antiseptic actions. The undoubted favorable actions observed clinically would appear to be better explained by their local anæsthetic and vascular actions.—Tr.]

Quite often the indication is to render the secretions more fluid and to facilitate their removal,—*i.e.*, to cause *expectoration.* This is the case when the secretion is very scanty or when, although profuse, it is extremely viscid, so that it is only with difficulty expelled by the actions of the ciliated epithelium or by coughing. Clinical experience indicates that the so-called expectorants often fulfil this indication more or less satisfactorily.

EXPECTORANTS

From the experimental side little is known of the manner in which expectorants act.

The experiments of *Henderson* and *Taylor* and those of *Rossbach* and *Calvert,* which latter two are open to many objections, are practically the only ones dealing with this subject.

As stated by *Purkinje* and *Valentin* in 1834, the ciliary movements of the cells of the bronchial mucous membrane are of great importance for the removal of mucus, especially from the smaller bronchi, in which coughing cannot produce any effective acceleration of the movements of the air. However, according to *Engelmann,* a very tenacious thick coating of mucus opposes an insuperable obstacle to the ciliary movements, and only when the secretion has become thinner and more fluid are these cells able to resume their function, provided that they have not lost their excitability and are still able to perform them, which is not always always necessarily the case in inflammations of the bronchial mucous membrane.

It is not known whether or not the ciliary movements may be stimulated by the expectorants, although *Virchow* in 1854 observed an active excitation of the previously motionless cilia after a direct application of potassium or sodium hydrate to the human tracheal mucous membrane, while strong ammonia stopped the movements without any primary stimulation. These two observations are, however, of no significance for estimating the effect of medicines, but perhaps those of *Engelmann* on the pharyngeal mucous membrane of the frog may be of some significance. According to this author, very small quantities of CO_2, ether, and ammonia stimulate the ciliary movements, while larger amounts depress them.

The unstriped bronchial muscles appear to play a decidedly more important rôle in the transportation of mucus from the alveoli and bronchioles up into the larger branchi, for there is no ciliated epithelium in the alveoli and the terminal bronchi. Both the alveoli and the bronchi contain unstriped muscles, whose changing tone is controlled by constricting and dilating nervous impulses which reach them through the vagus. This innervation, and, as will be seen later, also the pharmacological reaction of the bronchial muscles, is very analogous to the conditions in the intestine, and it is very possible that these organs also are capable of ascending peristaltic movements. In this fashion lumps of mucus might be moved upward in the narrowest bronchi (*Gerlach*). *Einthoven* observed spontaneous rhythmic contractions of the bronchial muscular apparatus independently of any nervous influence, but he did not conduct any investigation to determine whether these were always simultaneous contractions of the whole system or whether they were alternating peristaltic movements. It is not improbable that such peristalsis may be accelerated or strengthened under the influence of some of the expectorants.

Salts as Expectorants.—All the salts of the sodium chloride group (see section on salt action) may exert some expectorant action and increase the secretion of mucus, for they are in part excreted

by the bronchial mucous membrane and thus may bring about the secretion of an increased quantity of water and (as occurs whenever secretion is increased) of alkaline carbonates. This increased alkalinity of the secretion would be accompanied by a diminution of its viscosity, for the tenacity of the mucus is diminished as its alkalinity rises. In practice some of these salts are much used for this purpose. Among these are sodium chloride (the waters of Wiesbaden and many other springs) and potassium iodide or potassium sulphocyanide, which is not harmful in thyroid disease. (See p. 400 for dangers of KI in thyroid patients.)

Ammonium chloride appears to be still better for this purpose, for, following its administration, traces of ammonium carbonate are perhaps formed in the bronchial mucous membrane, and this has a special power of liquefying mucus and stimulating the ciliary movements. Its use in combination with soothing licorice preparations may therefore be understood. The alkaline carbonates in Ems water and many other mineral waters act in a similar fashion.

NAUSEANT EXPECTORANTS

Besides the salts mentioned, emetic drugs, especially apomorphine, ipecac, and antimony salts, produce a similar stimulation of the bronchial secretions when they are given in small non-emetic doses (see p. 179). This is probably a symptom of the first stage of their emetic action, which causes the striking increase of secretions which accompanies the nausea induced by larger doses. With apomorphine the action is a direct one, with ipecac, antimony, etc., a reflex one, on the centres controlling the secretion of the bronchial mucous glands, for these glands are affected readily, and often, especially in children, even more readily than are the sweat-glands, by drugs like pilocarpine, which are specific secretory excitants.

Moreover, inasmuch as with more pronounced emetic action the vagus innervation controlling emesis is excited, it may be that, in the first stages of their action, this vagus stimulation may cause the peristalsis in the smaller bronchi to become more active. This may at least be considered as possible.

Apomorphine hydrochloride in corresponding dosage appears to act more promptly and energetically than ipecac or antimony, but its action seems to be less lasting. It may be given several times daily to adults in doses of 2–10 mg. Alkalies should be avoided when this drug is prescribed.

Ipecac may be administered in various forms in dosage of 0.05 to 0.2 gm. to adults and 0.01–0.1 gm. to children. It is often combined with opium for the purpose of relieving a harrassing cough, but it is questionable whether this combination is a good one, for presumably morphine will depress the bronchial peristalsis (*Brodie* and *Dixon*).

Antimony and potassium tartrate, 2–10 mg. several times daily, may irritate a susceptible stomach mucous membrane. This is not

likely to occur if the sulphate of antimony be used, for this preparation is entirely insoluble in water, and in the acid gastric juice is changed only gradually into the active antimony oxide (see Emetics).

Senega and *quillaja* bark act as expectorants in a fashion not clearly understood, but in both saponins are considered to be the effective constituent. According to *Henderson* and *Taylor,* senega produces expectoration reflexly by its action on the stomach, as do ipecac, tartar emetic, and ammonium chloride.

Saponin is a name given to a large number of non-nitrogenous substances occurring especially in the bark and roots of numerous plants. They are characterized by their glucosidal nature and by their property of aiding in the formation of soapsuds, and are mixtures of various substances which are chiefly colloidal and which have not yet been chemically defined (quillaic acid, sapotoxin, sarsaparin, parillin, etc.). As a general rule, they are strongly cytotoxic and, when injected subcutaneously, intensely irritating. When injected intravenously, they cause hæmolysis, severe inflammation, enteritis and depression of the central nervous system. The epithelium of the mucous membrane of the alimentary canal is, however, very resistent to saponin and completely prevents saponin poisoning, as it does not permit the passage of altered saponins into the blood.

The resistance of the epithelial cells to saponin has been especially well demonstrated by *Lhomme's* observation that the ciliary movements in the frog's œsophagus were not disturbed by the application of concentrated solutions of saponin, even in the course of hours. The only effect on the mucous membranes, therefore, is a slight irritation of their sensory secretory mechanism. Tickling and increased secretion of mucus and saliva occur when these substances are taken into the mouth and throat. It is not known whether the increase of bronchial secretion is due to reflex action produced in this way or whether it is caused by an increase tendency to clear the throat or to cough. *Calvert* found that the bronchial secretions were inhibited after the intravenous injection of saponin, but such an experiment is not at all adapted to explain the therapeutic effect of saponin taken by mouth, for, when thus administered, it does not pass into the blood.

Theoretically it is of interest that the toxic action of saponin on the red blood-cells, and probably also on other animal cells (*Ransom*), is explained by its chemical affinity for cholesterin, the constituent of the cells which is chemically affected by the saponins. After saturation with cholesterin, saponin is no longer toxic to the red blood-cells, and consequently the blood-plasma, which normally contains a certain amount of cholesterin, protects the red cells against a limited amount of saponin.

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PARALYSIS AND SPASM OF THE GLOTTIS

Normal functioning of the glottis is necessary for normal respiration. In paralysis of this organ a valve-like closure of the vocal cleft may occur during inspiration, while, in spasm of the glottis, it is self-evident that closure of the vocal cleft will prevent both inspira-

tion and expiration. Except opium or morphine, which as a rule relieve spasm in catarrhal laryngitis or croup, we know of no pharmacological agents which will directly affect the laryngeal muscles and which are able to relieve their spasmodic contractions.

BRONCHIAL SPASM

Another obstruction to the ventilation of the lungs may result from spasm of the bronchial muscles, usually associated with the so-called *asthma nervosum,* which probably in most cases is due to an abnormally increased reflex excitability of the bronchial vagus centre (*Brodie* and *Dixon*). This reflex may be excited by stimuli in the sensory nerves of diseased bronchial, tracheal, and nasal mucous membranes. As a result of the spasmodic contraction of the smaller bronchi, the lungs become abnormally distended or inflated, for in inspiration the pressure of the atmosphere can still overcome the increased resistance, but in extirpation the limited elasticity of the lungs and the pressure of the expiratory muscles are not sufficient to do this. Therefore the quantity of residual air must increase with each respiration.

TREATMENT OF ASTHMA

Such an asthmatic attack may be relieved either by blunting the excitability of the central reflex mechanism—for example, with chloral hydrate or similar drugs *—or by depression of the vagus nerve-endings in the bronchial muscles. This latter effect may be induced by inhalation of ether or chloroform, as *Brodie's* and *Dixon's* experiments on animals clearly showed, but this has not been therapeutically attempted [? Tr.]. Bronchial spasm may often be satisfactorily relieved by drugs having the specific power of rendering the vagus nerve-endings—unfortunately, not only in the lungs—unexcitable.

The alkaloids of the atropine group, and lobeline, which closely resembles nicotine in its actions (*Edmunds*), are the best of these. According to *Brodie* and *Dixon,* the action of atropine is more lasting than that of lobeline.

Since the middle of the last century, *stramonium* leaves, *belladonna, hyoscyamus,* and *lobelia* have been recommended as remedies for various spasmodic affections, and especially for bronchial asthma. Extracts of these drugs and the smoke of their smouldering leaves or the salts of atropine have all been employed for this purpose. If asthma cigarettes exert any curative action, it must be due to the small quantities of atropine salts † which are carried along mechanically in the inhaled smoke and thus reach the pharynx and lungs (*Hirn u. Netolitzky*).

* Urethan is stated by *Brodie* and *Dixon* (loc. cit.) to relax the bronchial muscles by a direct action on them. If this be correct, the drug should be a useful asthma remedy, for its hypnotic action is comparatively slight.

† According to *Günther,* the smoke of a cigarette containing 4.0 gm. of stramonium leaves contains 0.4 mg. of atropine.

Atropine (1/20–½ mg. several times a day), which is contained in the first three drugs mentioned and its congeners (see Atropine group, p. 154), as also lobeline, from Lobelia inflata (Indian tobacco), possess the physiological property of depressing the motor nerve-endings of the vagus in the lungs, so that the bronchial muscles relax and the dilated bronchi no longer present an abnormal resistance to the expired air. As at the same time these drugs stimulate the respiratory centre (*Dreser*), a marked improvement and strengthening of the respiration follow their administration.

In addition, excessive bronchial secretion, which often plays a part in exciting attacks of asthma, is lessened by these drugs. When, however, sudden vasomotor disturbances, such as congestion of the bronchial mucous membranes, are responsible for the attack,—as, for example, in the asthma of hay fever,—these drugs, as may be well understood, are without effect. [As a matter of fact, the asthma in hay fever is probably due, in part at least, to spasm of the bronchial muscles, which may be secondarily caused, and clinical experience has demonstrated that marked relief is often obtained by the use of atropine or similar drugs in asthma of this type.—Tr.]

It is claimed that opium smoking and the inhalation of the smoke from smouldering paper impregnated with saltpetre are of value in bronchial asthma. Such smoke contains varying quantities of carbonates and nitrites in addition to the usual gases present in smoke. Under some conditions a favorable influence may be expected from the nitrites, but this will hardly be the case in bronchial asthma, the condition now under discussion. This will be more likely to occur in angina pectoris, which is occasionally mistaken for bronchial asthma. [Here again clinical experience is not altogether in accord with the opinion of the author. The translator is confident that he has occasionally, though rarely, seen unmistakable relief secured by the use of nitrites in cases of undoubted bronchial asthma.—Tr.]

[Epinephrin.—The marked relief following the subcutaneous injection of epinephrin (0.5–0.7 mg.) in asthma is so striking and well known that it should be mentioned here. Plethysmographic experiments, completed in 1911 in the laboratory of *H. Meyer,* demonstrate that this drug causes an excitation of the sympathetic nerve-endings here just as in other organs (see p. 141) and produces a relaxation of the bronchial muscles. A number of blood-pressure observations made on such patients, by the translator and by *I. I. Lemann,* have shown that the relief of the asthmatic attack following the injection of epinephrin is not necessarily accompanied by any rise in the blood-pressure. As a matter of fact, the blood-pressure occasionally rises, but more often remains constant or falls. The fall in blood-pressure, when it does occur, is apparently due to the relief of the dyspnœa and cyanosis. It has been claimed by various authors that the oral administration of epinephrin also affords relief in asthma. The translator from his own experience can, however, report only failures to

confirm these statements. In a number of cases, after oral administration had failed to give any relief, the subcutaneous administration promptly stopped the attack. Unfortunately, in several of the author's cases, after frequent repetition of the administration during a number of months, the treatment became ineffectual.—Tr.]

[Iodides.—No discussion of the pharmacology of asthma or bronchial spasm is complete which does not include some consideration of the action of iodides in these conditions. Clinical experience has demonstrated that in a large proportion of cases of true bronchial asthma the daily ingestion of fifteen to thirty grains of iodide of potash results in a more or less pronounced and unmistakably beneficial effect on the frequency of the attacks. While some of this benefit might be explained as the result of the expectorant action of the iodide (see p. 343), there is another probable explanation of it which, as far as the translator has been able to learn, has not yet been suggested. As will be discussed later (p. 354 ff.) the thyroid gland exerts an active effect on the sympathetic system, perhaps in the sense that it acts as a hormone on the chromaffinnic organs. Further, it is established that, at any rate under many conditions, the administration of the iodides causes an increase in the functional activity of the thyroid. Consequently it appears at least plausible that the favorable effects of the regular ingestion of iodides are to be attributed to an increased sympathetic tone brought about through increase of thyroid function. Otherwise expressed it might be stated that the daily use of iodides may in this respect have similar effects to the constant administration of minimal doses of epinephrin, which we have just seen is a most efficient means of relieving the condition of bronchial spasm. A further pharmacological deduction would be that possibly the administration of thyroid substance would be a more direct way of attaining this end.—Tr.]

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3. **Disturbance in the circulation in the lungs**, such as stasis resulting from cardiac insufficiency, may markedly interfere with the respiration and cause dyspnœa. The blood accumulating in the pulmonary capillaries distends them and causes rigidity of the lungs (*v. Basch's* "Lungenstarre"), the power of excursion of the lungs being diminished so that the renewal of air is seriously interfered with. The increased CO_2 tension in the blood-vessels resulting from this condition, then in its turn causes subjective dyspnœa with violent but ineffectual attempts to breathe. In cases of cardiac insufficiency the respiratory disturbances may be relieved by the relief of the disturbances of compensation resulting from the administration of drugs of the digitalis group.

The acute dyspnœa of exertion, such as occurs with healthy hearts after running, mountain climbing, etc., may be prevented by small doses of caffeine, 0.25 gm., taken about two hours beforehand (*Parisot*).

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CHAPTER X

PHARMACOLOGY OF THE RENAL FUNCTION

PHYSIOLOGY OF DIURESIS

The renal secretion of the healthy mammal is an albumen-free, dilute aqueous solution of the products of metabolism and of substances which after penetrating into the body are not utilized or retained but simply pass through it.

Available Water Necessary for the Secretion of Urine.—The first condition necessary for the formation and excretion of urine is the presence of available water,—*i.e.*, water which may be given up by the blood. As the normal water content of the blood is retained with great tenacity, it is essential that there be a certain, although slight, excess of water in the blood, a temporary hydræmia, if the giving up of water—*i.e.*, diuresis—is to occur.

In the blood-plasma the water is combined with its dissolved crystalloids and with colloids (proteids) in a state analogous to that of the "Quellungs" water, *i.e.*, intramolecularly imbibed water, in a gel or jelly. Just as in a jelly, a certain portion of the "Quellungs" water of the blood may be readily squeezed out by pressure. As, however, the concentration of the proteid increases the tenacity of the combination between the water and the proteid, the "Quellungs" pressure, rapidly rises, and very quickly becomes so great that even the highest pressure possibly available in the kidney can squeeze no water out of the blood. Superfluous water, introduced with food or entering the blood from the various cavities of the body and from the tissues, is under ordinary conditions readily excreted. In case these sources fail to supply extra water, a very small portion of the water normally present in the blood may be excreted, but the kidneys can under no conditions excrete what remains.

Importance of Sufficient Blood-pressure.—It may be considered as established that the water of the urine is excreted chiefly in the vascular loops of the glomeruli. For this to occur, the blood-pressure in them must be sufficient to overcome not only the hydrostatic pressure in the uriniferous tubules and ureters, but also the combination between the water and the dissolved colloids, the "Quellungs" pressure, of the blood-plasma. Under normal conditions, according to *Starling*, this equals about 30 mm. Hg, and, as a matter of fact, urinary secretion usually ceases when the blood-pressure falls much below 40 mm., and, within physiological limits, increases almost proportionately with the rising blood-pressure (*Goll*). (See Fig. 40.)

If, on the other hand, the blood is artificially made markedly hydræmic, its "Quellungs" pressure becomes low or practically zero. This occurs, for example, during the continuous intravenous infusion of isotonic sodium chloride solution, and under these conditions water may be secreted in the urine with a minimal

blood-pressure, which is just sufficient to maintain the blood flow (*Gottlieb u. Magnus*). *The process is therefore fundamentally comparable to a filtration or a transudation.*

THEORY OF URINARY SECRETION

This conception forms the essential portion of *Ludwig's* theory of urinary excretion, and was first deduced by *Bowman* from anatomical facts and later by *Ludwig* from the above-mentioned experimental data. According to it, in the glomeruli there is expressed from the blood a "colloid-free" filtrate containing water and dissolved crystalloids such as urea, salts, etc. As this passes down through the uriniferous tubules it undergoes a concentration, the water being reabsorbed into the blood by osmotic action, which flows from the glomeruli to the thick network of capillaries surrounding the tubules.

On account of a number of objections, *Heidenheim* has offered, as a substitute to this essentially mechanical conception, the so-called secretion theory, according to which the water is not expressed from the blood as a result of pressure, but is secreted by a specific cell activity, while the solid constituents are actively secreted by the epithelium of the uriniferous tubules in a manner analogous to that in which the secretion of other true glandular epithelium occurs.

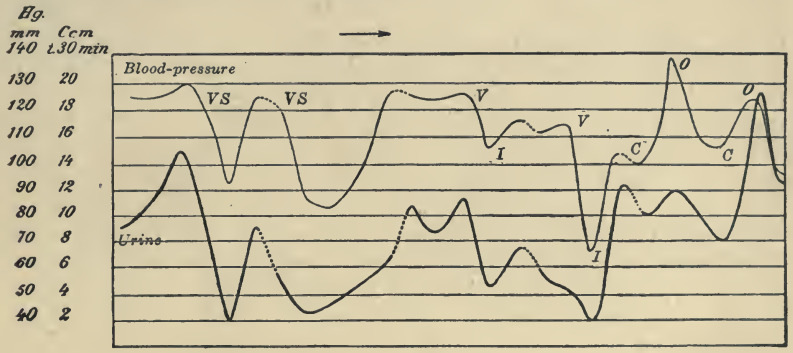

FIG. 40.—*VS* = vagus stimulation; *V* = venesection; *I* = infusion of blood; *C* = closure, and *O* = opening of the carotid and crural arteries. Urinary excretion in dog under varying blood-pressure (*Goll*).

Heidenheim's conception provides without difficulty for all the phenomena observed in normal and altered renal secretion, explaining everything by an adaptation of the kidney to the needs of the organism. It renounces, however, any attempt to analyze the process, and especially any attempt to differentiate the influence which may be exerted on the excretion of urine by varying physiological or pathological conditions. Such are, for example, the effect of diuretics, such as the salts, calomel, caffeine, etc.

The functional processes of all other glands of the body are independent of direct physical and of almost all chemical influences. They are specific processes, directly or reflexly under nervous control, and may be analyzed chiefly in respect to their dependence on nervous control. On the other hand, we know of no specific innervation for the kidney, but we do know that there are certain physical factors, dependent on the composition of the blood and on its circulation through the kidneys, which are of decisive importance for its activity.

However, the investigations of the last decade have clearly shown that the formation of the urine cannot yet be completely or even in greater part explained physicochemically.

It will therefore be our task to find out how far we may follow, or recognize as possibly effective, the influence of physical-chemical factors on the secretion of urine under abnormal conditions (for example, alteration of the renal circulation), and especially on the alterations of function resulting from the action of pharmacological agents, and to learn how far on the other side we must assume specific secretory processes which are not susceptible to further analysis.

The Importance of the Amount of Blood Flowing through the Kidney.—If the blood flows slowly through the glomerular vessels (on account of low pressure or decided resistance), or should it stagnate there,—as, for example, when the renal veins are ligated,—the secretion of urine ceases, even though, in the later case, the pressure in the glomerular loops must rise to its maximum. This fact was especially brought forward by *Heidenheim* as an objection to the theory of pressure filtration and advanced as an argument for the correctness of the secretory theory. However, the filtration theory demands, besides an adequate blood-pressure, that the blood flow in these vessels shall be rapid enough to supply to them constantly fresh blood in sufficient quantities, for otherwise the blood, stagnating in the glomeruli, must, on account of loss of its available water, necessarily instantly become so concentrated that its "Quellungs" pressure will rise so high that, even under any attainable blood-pressure, no appreciable amounts of water may be expressed, and the secretion of urine must therefore cease. *Diuresis, therefore, under all conditions demands an adequately rapid changing of the blood in the glomerular vessels,—i.e., an adequate circulation of blood through the kidneys.* It is apparent that this factor is of even greater moment for diuresis than is the blood-pressure.

Excretion of Urea, NaCl, etc., in the Glomeruli.—Most of the crystalloids dissolved in free form in the blood do not cause any appreciable osmotic resistance to the passage of the urinary fluid through the walls of the glomeruler loops (see p. 384 ff.), and therefore do not hinder the excretion of water. On the contrary, diuresis generally increases when larger amounts of these substances are contained in the blood (*Tamman*). From this it is necessarily deduced that these substances are excreted in the glomeruli together with, and at the same time as, the water (*Hermann, Treskin, Richet, Loewi, Magnus*). As a matter of fact, their excretion rises and falls almost proportionately with the amounts of water excreted, they being apparently swept along with it.

Pathological Retention of Salts.—However, what has been said above is subject to an important limitation, for in experiments on animals it has often been observed that, in long-continued experiments in which intravenous saline infusion has been given to cause diuresis, the diuresis after a time diminishes and the kidney retains more and more, not only of the water but also of the sodium chloride infused.

Moreover, it is well known that in certain pathological conditions in man, chlorides are very sparingly excreted, and that the administration of salt, instead of increasing diuresis as it does normally, actually decreases it (*Widal* and *Javal, Grüner, Schlayer, Hadinger* and *Takayasen,* and a review in *v. Noorden's* Pathology of Metabolism, vol. 1).

Impaired Permeability of the Glomerulus.—In order to understand this phenomenon we must, in our consideration of the filtration theory, add to it the almost self-evident premise that the permeability of the living filter membrane in the glomeruli for free crystalloids or ions is neither unchangeable nor without limitation, but that, on the contrary, the size of the hypothetical pores changes under different nervous, mechanical, or direct chemical influences, and that therefore many substances in solution can pass through them, sometimes more and sometimes less readily and sometimes not at all.

It is well known that the permeability of this membrane for proteid is subject to variations. Under normal conditions proteid does not pass through the human kidney in appreciable amounts, but under certain conditions very slight changes in the circulation are sufficient to render the glomeruli permeable to albumen. This occurs, for example, in orthostatic albuminuria (*Jehle*). Moreover, experimental analogies for the variable permeability of filters are not lacking. For example, filters impregnated with gelatin are rendered more or less permeable for different substances, according to the gelatin concentrations used (*Bechhold*).

Secretion by the Tubular Epithelium.—While the excretion of many of the soluble constituents of the urine in general occurs as a result of physical phenomena, it is known that the secretion of some other substances, among them *uric acid and many salts of the heavy metals,* occurs in a different fashion and does not appear to stand in any recognizable relationship with the amounts of urine excreted. Apparently they are excreted by the functional activity of the epithelium of the tubules. *Their secretion must therefore be considered as due to a secretory activity incapable of closer analysis,* just as is the case with secretions in other true glands.

Concentration of the Glomerular Filtrate.—The urine flowing from the kidney is usually more concentrated than a true filtrate from the glomeruli could possibly be. This higher concentration is, however, readily comprehensible if in the secretory theory it is premised that the solid constituents of the urine, including urea and the salts, are secreted by the uriniferous tubules and mixed in with the dilute glomerular filtrate. As qualitatively and quantitatively this secretion is constantly changing with the needs of the organism and the momentary condition of the secreting cells, a varying composition of the urine is to be expected. As, however, as was mentioned above, the crystalloids appear in the urine in quantities nearly proportional to the amounts of water, and as their excretion by physical means (such as filtration or transudation in the glomeruli) may be considered as established, it would be necessary to assume the occurrence of an

additional secretion of the same crystalloids by the epithelial cells of the tubules in order to bring about the final concentration. This complicated hypothesis need, however, not be adopted if it be assumed that the concentration of the urine is brought about by a reabsorption of water, similar to that which takes place in the large intestine during the concentration of its liquid contents.

In the human alimentary canal about 4000 c.c. of water are secreted in every 24 hours, and of this about 3900 c.c. are reabsorbed. In order to secrete about 30 gm. of urea in 24 hours, 50 litres of fluid must be filtered in the glomeruli from blood containing about 0.6 per cent. of urea, and of this about 48 litres must be reabsorbed in the long, sinuous course of the uriniferous tubules. Between 500 and 600 litres of blood flow through the kidneys in 24 hours, of which about one-tenth would have to be expressed as a filtrate to satisfy the Ludwig hypothesis, There is nothing improbable in such an assumption. On the contrary, the appreciably narrower lumen of the vas deferens as compared with that of the vas afferens may be considered as a proof that a considerable portion of the fluid of the blood-plasma entering the glomerulus is removed in some fashion,—in other words, is excreted.

Selective Reabsorption.—The reabsorption of water in the tubules cannot be explained physicochemically any more than that of certain of its crystalloid constituents. However, numerous earlier investigations * rendered it probable, while the most recent observations (*Nishi*) have certainly proven that the tubules are able to absorb not only water but also dissolved substances, especially the readily diffusible crystalloids.

The normal urine of rabbits and dogs contains no recognizable amounts of sugar. In accordance with this, *Nishi* found that normally the medullary portions of the kidney contained no sugar, while it was constantly present in the cortical portion, but, if in any fashion glycosuria were induced, sugar was found in the medullary portions. Inasmuch as the minimal amounts of sugar contained in the blood could not influence the quantitative determination of the sugar present in kidneys from which the blood had been thoroughly removed, these observations permit the conclusion that sugar is excreted in the cortex, but that under normal conditions it disappears again in the medulla and that it is reabsorbed there. Only when larger amounts are excreted in the glomeruli and when the reabsorption is incomplete does sugar appear in the urine (*Pollak*).

Combined Effect of Filtration, Secretion, and Reabsorption.—In any case it may be maintained that, generally speaking, the extent of the filtration taking place in the glomeruli determines the total quantity of the urine secreted, while the momentary composition of the urine is determined by a selective secretion or reabsorption in the tubules.

Secretion of Water by the Tubules.—In addition to this power of free absorption, the tubules probably also possess the faculty of excreting water under some conditions and adding this to the glomerular filtrate. This would appear to be analagous to the behavior of the sweat-glands, which also excrete almost pure water in amounts which vary according to their blood supply and the water content of the

* *v. Sobieranski, Halsey* and *Meyer, Cushny, Loewi, Gottlieb* and *Magnus, Grünwald, Sollmann;* see latter for lit.

blood. The secretion of a very dilute urine, the osmotic concentration of which does not equal that of the blood, which is observed after free drinking of water, in diabetes insipidus, etc., can hardly be explained on any other assumption (*Frey*). Moreover, there can be no doubt that there is a certain antagonism in the behavior of the capillary system of the glomeruli, which is supplied by the vasa afferentia of the renal artery, and the capillary system of the tubules, which receive their supply from the vasa efferentia and the arteriolæ rectæ. If the vasa afferentia dilate, the vasa efferentia, and perhaps also the arteriolæ rectæ, contract. Thus the pressure and flow in the glomeruli are increased while in the tubular capillaries they are relatively diminished, and *vice versa*. In accordance, therefore, with such variable conditions, filtration in the glomeruli or secretion in the tubuli may preponderate (see Fig. 41).

It is self-evident that both of these vascular systems are, like all other blood-vessels, under the control of the nervous system, but we have little exact knowledge of this mechanism. The oncometric determination of the volume of the kidney serves as a means of esti-

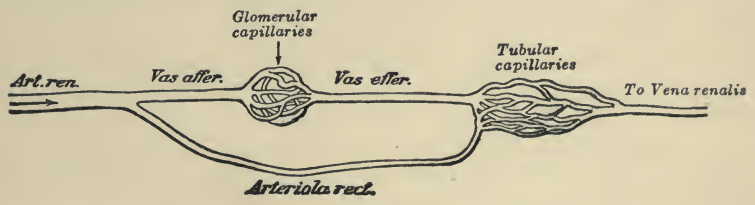

Fig. 41.

mating the blood flow through it, if the outflow of venous blood and of urine be unhindered. Further, the color of the venous blood allows an approximate estimation, for with increased blood flow the blood appears light red through the wall of the vein, while with diminished blood flow the blood appears darker.

According to *Tigerstedt*, during moderate diuresis blood amounting to 80 per cent. of the kidney weight flows through it in one minute; with greater diuresis as much as 140 per cent. If both kidneys weigh 300 gm., this would amount in man to 345–600 kg. in 24 hours.

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FACTORS CONTROLLING DIURESIS

These factors mentioned as being of moment for diuresis,—namely,

Hydræmia, with its influence on "Quellungs" pressure and the osmotic tension of the blood;

Blood-pressure and rapidity of the blood flow in the renal vessels;

Reabsorption and secretion in the tubules, may be pharmacologically influenced at times in common and, in so far as they do not depend upon one another, at times separately.

Alteration of the Water Content of the Blood

1. **Hydræmia** necessarily results from drinking liquids or eating food containing much water. The water which is drunk dilutes the blood to a moderate degree (*Buntzen*) and is excreted in the urine in the course of 6–7 hours (*Falck*), and, as water containing carbonic acid is absorbed more quickly (see p. 173), it is excreted more rapidly. After this has occurred the amount of water in the body remains the same as it was previously, for diuresis, thus stimulated, results only in a washing out of the body and a dilution of the urine. Such dilution of the blood may be beneficial in chronic poisonings and in conditions of abnormal metabolism, while increased diuresis may be useful in disease of the urinary tract, such as pyelonephritis, cystitis, or uratic concretions.

It is clear that the same indication may be met, in case of need, by subcutaneous or intravenous administration of isotonic saline solution.

If, on the contrary, it is desirable to remove water from the body by causing increased diuresis, the necessary hydræmia must be obtained at the expense of the water contained in the tissues. A transudation of the lymph-plasma into the blood will do this, for the lymph contains only about one-third as much proteid as does the blood-plasma. This occurs, for example, after extensive blood letting, which may therefore have a diuretic effect (*Leube, Geelmuyden, Laache*).

The Production of Hydræmia by the Use of Salts.—The osmotic tension of the blood may be increased by the administration of substances which penetrate through the cell membranes only slowly or

not at all, thus attracting the water from the tissues into the lymph and blood. This is another means which may be employed to produce hydræmia. It is a self-evident prerequisite for the value of this procedure that the substances employed can readily pass through the glomerular membranes and thus do not oppose any osmotic resistance to filtration at this point. If they then pass into the tubules with the water from the blood, they will, by their osmotic pressure, prevent the reabsorption of the water, in this way, too, increasing the amount of urine.

"The diuretic salt action," according to this conception, is then produced in two fashions,—first by causing hydræmia, and second by inducing a *"diarrhœa in the tubules."* Probably a third factor is active here, an *"Entquellung"* * of the blood-plasma by the salts, the blood colloids being thus deprived of some of their water, which water is rendered more readily filterable by being freed from the "Quellungs" pressure which opposes the filtration (*Hoppe-Seyler, Runeberg*). Colloids like gum arabic or gelatin (0.6–1.0 gm. per kilo), when injected intravenously, inhibit diuresis, but if sodium chloride be subsequently injected, free diuresis occurs as a result of the "Entquellung" of the colloids. Moreover, the flow of blood through the renal vessels is facilitated by addition of salt to the blood, for the renal tissues shrivel up somewhat as a result of losing part of their water; thus the lumen of the blood-vessels becomes wider (*Sollmann*).

The diuretic effect of the salts is, other things being equal, inversely proportional to their power of diffusion. As a matter of fact, the immediate diuretic effect when solutions of the but slightly diffusible Na_2SO_4 or $NaHCO_3$ are introduced into the blood is markedly greater than occurs after injection of equal amounts of isosmotic solutions of NaCl or sodium nitrate, which diffuse much more readily into cell membranes (*Halsey, Magnus, Cushing, Münzer,* and others).

In such experiments, as should be expected, the poorly diffusing sodium sulphate is excreted in larger amounts and with greater rapidity than is the readily diffusible sodium chloride. In other words, it is more "harnfähig"† than NaCl, for during the relatively long passage through the uriniferous tubules the Na_2So_4 is absorbed to a much slighter extent than is the NaCl. Diuresis caused by Na_2SO_4, therefore, is more intense and passes off more rapidly than that caused by NaCl.‡

For practical use, however, only substances relatively easily absorbed from the intestines—*i.e.,* of the salts, only the readily diffusible ones, especially NaCl and potassium nitrate and acetate—may be

* By this apparently untranslatable German term is meant the attraction to and combination with the salts of a portion of the water previously firmly combined with the colloids of the plasma.

† Harnfähig means readily excreted in the kidney.

‡ [Sodium sulphate has a greater power of attracting the water from its combination with proteid and consequently causes a greater hydræmia.—Tr.]

administered for this indication.* Of these the acetate after absorption is changed in the blood into the less diffusible and, therefore, diuretically more active carbonate. This would appear to account for the preference given it as a diuretic.

Contraindications.—It is necessary, however, again to emphasize the fact that in many cases of disease the administration of sodium chloride does not increase but, on the contrary, diminishes the secretion of urine, even though the blood is rendered more hydræmic as a result of the attraction of water into it from the tissues, which occurs when the sodium chloride in the blood is increased. In such cases it would appear that the glomerular membrane has become relatively impermeable for NaCl, and that therefore this salt offers an osmotic resistance to the excretion of water; here, by administering a diet poor in salt, the osmotic partial pressure of this salt may be lowered and an increased urinary secretion result (*Nils Finsens*).

Urea as a Diuretic.—The same effect may also be obtained at times by the administration of substances which act like salts but for which the glomerular membrane is still permeable,—for example, by the administration of urea, of which 10 gm. are approximately isosmotic with 5 gm. NaCl or 8 gm. potassium acetate. According to this, it would be necessary to administer at least 20–40 gm. of urea daily to produce a pronounced effect (*Klemperer*). Urea, while passing readily through the intestinal epithelium and permeating rapidly into the blood-cells, passes into the muscle-cells and the epithelial membrane of the urinary tract with great difficulty (*Gryns, Overton*). In the blood and tubules, therefore, it has a strong power of attracting water to itself. Such elective semi-permeability is often met with in the organism, although it cannot be explained chemically.

Sugars as Diuretics.—Glucose, and, in a greater degree, the poorly diffusing milk-sugar, when taken in amounts of 100–200 gm. dissolved in as little water as possible, are stated to cause diuresis and absorption of œdema. When they pass into the blood, they cause, presumably by osmotic action, a temporary hydræmia (*Meilach*). If they pass into the urine, as in diabetes mellitus, they must, like the salts, hinder reabsorption in the tubules and produce, as it were, a "renal diarrhœa."

Mercury as a Diuretic.—Finally, hydræmia may be induced by mercurial preparations, especially by calomel, of which doses of 0.2 gm., several times daily, produce a marked diuresis, especially if the tissues are œdematous and diarrhœa is prevented by opium.

According to *Fleckseder* (unpublished experiments), the hydræmia caused by calomel is induced as follows: The increased secretions and the partially prevented reabsorption in the small intestine, together with the actively stimulated peristalsis, cause the accumulation in the

* [*M. Fisher* believes that the saline cathartics as ordinarily administered are absorbed in sufficient amounts to cause a hydræmia and thus to cause increased diuresis.—Tr.]

large intestine of large amounts of fluid. If this large quantity of fluid is not rapidly expelled from the colon, but remains there for a time, it is absorbed by the mucous membrane of the large intestine and dilutes the blood, which in the meantime, by attracting water from the œdematous tissues to replace that lost to the intestine, has already regained its original concentration. The blood which has thus been rendered hydræmic then gets rid of its extra water through the kidneys, and a marked diuresis occurs.

The diuretic effect of the mercurials appears not to depend at all on, nor to be related in any way to, the very harmful action exerted on the renal epithelium by its soluble preparations, such as corrosive sublimate.

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2. **The rate of flow and the pressure of the blood in the renal vessels** depends, on the one hand, on the resistance in them and, on the other, on the functional performance of the heart and on the general blood-pressure.

Stasis.—The resistance to the blood flow in the kidney may be a hindered outflow from the renal veins, as, for example, in cardiac stasis, in which case an improvement of the cardiac function relieves the oliguria (see p. 296). The outflow from the renal veins may also be hindered by a collection of fluid in the abdominal cavity, and, if the fluid be removed by aspiration, the previously halting secretion of urine may become normal again. Further, if the amount of fluid in the abdomen be diminished by other means,—for example, by the removal of large amounts of water by way of the intestines, as a result of the administration of Epsom salts or of drastic cathartics, or by excessive sweating,—the pressure on the vena cava is lessened and, as a rule, improved diuresis results. In this indirect sense, cathartics and sudorific drugs may, under pathological conditions,

increase the secretion of urine, in place of diminishing it as they do under normal conditions [see footnote, p. 356.—Tr.].

Renal Vasoconstriction.—Resistance to the blood flow through the kidney may also be due to a more or less pronounced contraction of the renal arteries and capillaries.

Our knowledge of the variations in the tone of the renal vessels is very imperfect. Sensory stimuli, especially those arising in the urinary tract, not infrequently cause long-continued reflex anuria, which probably is due to a tonic contraction in some portion of the renal vascular system, whether in the glomerular vessels or in the vasa efferentia or in the capillaries is uncertain. Moreover, in many forms of acute nephritis with scanty secretion of urine, it is possible that the abnormal contraction of individual groups of the renal vessels may be the cause of the oliguria. Finally, it is conceivable that the calibre of the uriniferous tubules may change and under some conditions oppose a high resistance to the passage of urine. The richness of the nerve supply in their membrana propria (*Disse*) speaks for the possibility that this may occur.

Indirectly the amount of blood flowing through the kidney may be roughly estimated, and the degree of resistance may be directly determined by the use of the oncometer if care be taken to prevent any hindrance to free outflow of the venous blood and urine; but this method gives no information about the distribution of the blood in the different renal vessels. It is possible, too, that dilatation of the vessels and the resulting increased blood flow may occur without any increase in the volume of the kidney, this occurring at the cost of other compressible parts of the kidney—for example, of the tubules—or as a result of an "Entquellung" or shrinking of the capillary epithelium (*Sollmann*). Consequently the rate of the blood flow through the kidney may not under all conditions be deduced from the changes in its volume (*Loewi*).

The renal vessels may be contracted as a result of reflexes from sensory stimuli, especially those resulting from cooling of the skin (*Wertheimer*). Drugs which, like strychnine, increase the reflex tone of the vasomotor centres, may also cause constriction of the renal vessels. However, this centrally induced vasoconstriction in the kidney is not a lasting one, being much less persistent than the constriction of the intestinal vessels, and after a short time the renal vessels again dilate. The blood forced from the other still contracted vascular systems will then flow so much the more freely through the kidney, and an active diuresis results. The effect of the renal vasodilatation following such reflex renal vasoconstriction is evidenced by the desire to urinate which is often experienced after, or even during, a cold bath. The peripheral action of epinephrin appears to produce a similar effect in the kidney. [With pituitrin this effect is still more pronounced.—Tr.]

RENAL VASODILATATION

Chemical influences of varying nature may cause dilatation of the renal vessels by a direct action on their walls.

Hydræmia of any type causes a dilatation of the renal vessels,

and therefore all agents causing hydræmia indirectly produce this effect.

It has been found that with the occurrence of hydræmia, no matter how occasioned, the volume of the kidney is regularly increased, and that the blood flows through it more rapidly and that, too, even after the kidney vessels have been isolated from central nervous influences by destruction of their nerves. Therefore, it would appear that the amount of water in the blood—or, otherwise expressed, the "Quellungs" pressure of the blood—exerts a direct influence on the tone of the renal vessels and in this way regulates the blood flow through the kidney in a purposeful manner (*Loewi*).

Almost All Substances Which are Excreted by the Kidney Cause Dilatation of Its Vessels (*Abeles, Grützner*).—The kidney is the excretory organ for most of those substances which simply pass through the body. Just as the intestine, in order rapidly to rid the body of many harmful substances, reacts to them with hydræmia of the mucous membrane, diminished absorption, increased peristalsis, and, in case of more powerful irritation, with free transudation, it would appear that almost all the substances foreign to the body which must be excreted by the kidney cause active vasodilatation in this organ and increased diuresis. *Many of these substances also, even in very small amounts, cause degenerative changes in the kidney, and thus, in spite of their powerful primary diuretic effect, are not useful practically or are perhaps directly harmful.* Cantharidin, formerly much used in the treatment of dropsy, acts in this fashion.

Other substances cause these degenerative changes only when they reach the kidney in large quantities or in high concentration, but are ordinarily harmless and may be used as mild kidney stimulants. In this group belong many, perhaps all, of the so-called *ethereal oils,* which are present in very small amounts in numerous drugs and which may well be responsible for the diuretic action attributed to many of them. Some of the substances mentioned above as inducing hydræmia, especially urea, and perhaps also *potassium nitrate,* appear also to possess a similar direct vasodilating action and the power of accelerating the blood flow in the kidneys.

Those narcotics, such as alcohol, amylene hydrate, paraldehyde, etc., which are excreted by the kidneys, may produce similar effects, but with them their specific narcotic action, which includes their power of lessening reflex actions, may also be of importance, especially in cases of reflex anuria (*Mori*).

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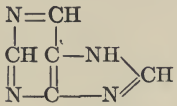
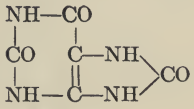
SPECIFIC RENAL VASODILATING DRUGS

Substances belonging to the purine group, caffeine, theobromine, and related substances, dilate the renal vessels in an entirely peculiar and elective fashion.

CAFFEINE, or theine, trimethylxanthine, occurs in the following proportions in various plants:

In coffee bean, up to 2 per cent.; in tea leaves, up to 4 per cent.; in cola nut, up to 2 per cent.; in guarana, up to 5 per cent.; and in Paraguay tea and other plants, in still larger proportions (*Goris et Fluteaux*). In pure state it forms shining silky crystals, very soluble in boiling water, but at 15° C. requiring 80 parts for their solution. In its chemical constitution it closely resembles theobromine and its isomer, theophylline, as also xanthine and uric acid, while synthetic chemistry has furnished a number of other closely related substances. All these substances are substitution products of the purin nucleus.


Purine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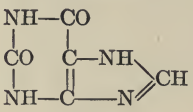
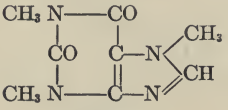
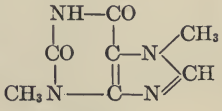
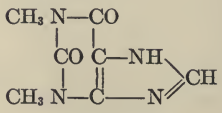

Xanthine


Caffeine


Theobromine


Theophylline

The diuretic effect of coffee, tea, and caffeine has long been known and used in therapeutics (*Bouchardat*, 1859). For a long time the views concerning the manner in which it caused diuresis were very contradictory. Some authorities—as, for example, *Riegel*—as late as in 1884 considered this to be an indirect action similar to that of digitalis, while others, among them *Curschmann* in 1885 and *Bronner* in 1886, as a result of their clinical observations, pronounced the caffeine diuresis to be independent of any cardiac and vascular action and attributed it to a specific stimulation of the kidney.

CAFFEINE

It has already been stated that caffeine exerts a marked influence on the circulation, but this effect is entirely different from that of digitalis, consisting of the following factors:

1. Stimulation of the vasomotor centres causing constriction of the arterioles, and, as a result, at times, an increase in the blood-pressure.

2. An influence on the cardiac function in four different ways: (a) Stimulation of the inhibitory vagus centre, causing retardation of the pulse. (b) Stimulation of the cardiac accelerating ganglia in the periphery, causing acceleration of the pulse; one or the other of these two effects preponderating as conditions or individuals may

differ. (c) An effect on the heart muscle, the relaxing power being diminished while the contractile energy is increased; as a result usually a diminution of the pulse volume of the heart and a fall in blood-pressure. (d) Dilatation of the coronary vessels.

If the vasoconstriction is the preponderating effect, the blood-pressure rises above the normal; but if the vasoconstricting centres are less excitable than usual or if they have been paralyzed by pharmacological agents such as alcohol, caffeine, as a rule, lowers the blood-pressure. However, in neither case would the actions of caffeine cause an increase of the blood flow through the kidney or an increased diuresis resulting therefrom, for, in case the blood-pressure is raised by caffeine, this is due not to acceleration of the blood flow throughout the body but to its retardation, just as is the case with strychnine. Therefore, only *when the insufficient blood flow through*

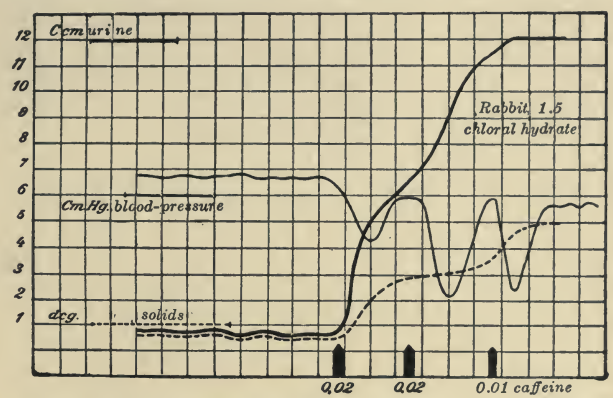


Fig. 42.—Effects of caffeine on the blood-pressure and renal secretion in the chloralized rabbit (*v. Schroder*).

the kidney and the halting diuresis is due to the fact that the heart is beating feebly, and therefore insufficiently supplying its coronary vessels with blood, can the general circulatory action of caffeine cause an increase in the secretory activity of the kidney.

Direct Action on the Kidney.—However, even when the heart is entirely healthy and receiving the optimal amount of blood, caffeine acts as a diuretic. To *v. Schröder* belongs the credit of having been the first to prove experimentally that caffeine diuresis depends essentially on a specific action in the kidney, by showing that its diuretic effects may actually be diminished and under some conditions entirely suppressed by the stimulation of the vasoconstrictor centres by caffeine, while, on the other hand, marked diuresis occurs when these centres have been depressed by chloral, paraldehyde, and similar drugs, or when their influence on the renal vessels has been prevented by section of the renal nerves.

Rost's investigations demonstrated, moreover, that the diuretic effect occurs only when considerable amounts of caffeine pass into the urine, and that consequently its seat of action lies in the renal parenchyma itself. In dogs, in which diuretic effects are obtained only by very large doses of caffeine, only 8 per cent. of the caffeine administered passes into the urine, while in rabbits, which react to relatively small doses with marked diuresis, more than 20 per cent. is excreted.

Although *v. Schroder* explained the diuresis caused by caffeine as due to stimulation of the secretory elements of the kidney to greater activity, it has not been possible to prove that such a specific stimulation of secretory activity occurs. In fact, its occurrence has been rendered improbable by the experiments of *Loewi,* who found that during phloridzin glycosuria caffeine increased the amount of urine secreted six- or sevenfold, while there was no increase in the amounts of sugar excreted, although the sugar is undoubtedly excreted by a specific secretory activity of the kidney. On the other hand, there are two other factors definitely established which are sufficient to account for the stimulation of renal secretions by caffeine. These are, in the first place, an *increased flow of blood in the kidney* and, secondly, *an inhibition of reabsorption in the uriniferous tubules.*

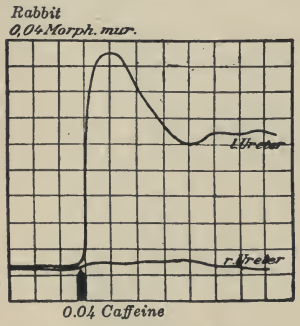


Fig. 43.—Effects of caffeine on the secretion of the normal right and the nerveless left kidney.

Increased Blood Flow.—Caffeine and other related substances under all conditions cause a dilatation of certain of the renal vessels, so that, as a rule, the total volume of the kidney is increased, as can be shown by the use of the oncometer. However, even when the volume of the kidney does not increase of its own accord, or when it is kept at a constant volume by firm encapsulation, it may be demonstrated that the blood flow through the kidney is markedly augmented by caffeine, for the blood in the renal veins which was previously dark in color now has the color of arterial blood (*Loewi, Fletcher, Henderson u. Loewi*). This effect is independent of the renal nerves, for it occurs even many weeks after their division and must therefore be due to an action on the muscles in the walls of the renal vessels. By such an actively augmented blood flow through the kidney the necessary conditions for increased diuresis are established. In accordance with this, it has been found that caffeine produces no effect on diuresis if the chief blood paths—that is, the vessels of the glomerular loops—are diseased and incapable of reacting, and that caffeine diuresis may still occur if the pathological changes have affected essentially only the tubular epithelium (*Schlayer*).

The second factor, the inhibited reabsorption, has not been absolutely proven, but has been shown to be extremely probable.

Inhibition of Reabsorption.—Evidence of this reabsorption was long ago furnished by the staining experiments of *Sobieranski*, who found that under the influence of caffeine the epithelium of the convoluted tubules lost the power of imbibing and staining with indigo-carmine, which after injection into the blood is excreted in large amounts in the urine and which under normal conditions is absorbed by these cells and stains them deeply.

These experiments indicated, in the first place, that this stain, although excreted in the urine, did not pass into it through the tubular epithelium, and, in the second place, that when caffeine had been administered this stain could no longer pass with the reabsorbed fluid into the epithelial cells as it does normally. Otherwise the nuclei would be intensely stained after caffeine just as is the case under normal conditions. It, therefore, would appear that caffeine inhibits reabsorption by lessening the power of the tubular epithelium to reabsorb substances from the glomerular filtrate.

Further support for this view is furnished by the experiments of *Hirokawa*, who found the osmotic pressure in the renal cortex very constant but varying within wide limits in the medulla, and that, in exact proportion to the concentration of the urine last secreted, it was many times higher here than in the cortex. Under the influence of caffeine, however, the molecular concentration in the medulla sinks nearly to the level of that in the cortex. This is to be explained most simply by the assumption that the cortical secretion or filtrate remains unconcentrated, which is equivalent to saying that the normal concentrating reabsorption of the urinary water fails to take place in the medullary portion. The observations of *Galeotti* and *Santa*, that only the cortical portion and not the straight tubules hypertrophy when compensatory hypertrophy of one kidney occurs, would indicate that the medullary portion—that is to say, the straight tubules—have no important secretory function. (For lit. see *Kapsammer.*)

Grünwald's observations on the excretion of the chlorides also point in the same direction. He found that rabbits poor in chlorides, which secrete urine containing no chlorides, may, by the administration of theobromine, be made to excrete them in the urine in such large amounts that they may die because of the loss of chlorides. Moreover, the chloride content of the renal cortex, the place where the chlorides are excreted, was found to be very constant and almost the same in animals whether they were rich or poor in chlorides, while the chloride content of the cortex was found to vary parallel with the chloride content of the urine and to be regularly increased when theobromine is administered. It appears that this is most probably due to the fact that theobromine causes a diminished reabsorption of the chlorides in the medullary portion of the kidney.

Other Actions of Caffeine.—Besides acting on the circulation and on the renal function, caffeine increases the general reflex excitability of the central nervous system and augments the functional capacity of the striated muscles. (See appropriate sections.) The increased reflex excitability may be observed in both cold- and warm-blooded animals after very moderate doses, while in severe poisoning in animals it may cause a reflex tetanus. In man the lesser degrees of this action express themselves by excitement, sleeplessness, marked palpitation, and sometimes also by diarrhœa and vomiting (*Kurschmann*).

As a Diuretic.—Caffeine, in doses of 0.1–0.3 gm. several times daily (0.5 gm. maximal single dose and 1.5 gm. maximal dose for 24 hours), or the readily soluble double salt caffeine and sodium salicylate, may cause very marked diuretic effects, provided that the

tissues or the body cavities contain sufficient fluid as in cases of œdema or exudation [provided also that the kidney is not so damaged that it cannot react efficiently.—Tr.].

In individuals with readily excitable vasomotor centres the diuretic effects of caffeine may be expected to be uncertain, for it stimulates these centres in a fashion analogous to, but much more weakly than, strychnine, and this central action may counteract the local vasodilating action in the renal arteries. In such cases combination with alcohol or similarly acting drugs may aid in producing the desired effect.

The diuretic action of theobromine and theophylline, which are chemically so closely related to caffeine, is even more reliable than that of caffeine, for they cause hardly any central stimulation.

Theobromine is very insoluble in water, and is therefore advantageously administered in the soluble but very alkaline double salt theobromine and sodium salicylate, diuretin, in doses of 0.5–1.0 gm. (6.0 gm. per diem), or as theobromine and sodium acetate, known as agurin, in like dosage. Disturbances of the stomach and intestines are more readily caused by these drugs, however, than by caffeine.

Theophylline, or *theocin,* is stated to be an even more powerful diuretic, especially in doses of from 0.2–0.5 gm., but it readily causes disturbances of the stomach, vomiting and diarrhœa, and in doses of 1.0 gm. per diem has occasionally caused violent epileptic attacks in epileptic patients (*Schlesinger*). Not more than 0.8 gm. of the pure theophylline or 1.5 gm. of its sodium acetate should be administered daily.

As theobromine and theophylline also exert the same peculiar action on the striated muscles as caffeine, one might be tempted to believe that the muscle action and the diuretic action are in some way due to a common cause. The parallelism of these two actions is, however, only an accidental one, and is not observed in a whole series of other synthetically prepared purine derivatives. Thus, acetylamidocaffeine, diacetylamidocaffeine, and caffeine methylendiamin hydrochlorate possess no action on the muscles and are in other respects practically without toxic action, while they exert the specific diuretic action in a high degree (*H. Meyer, unpublished experiments*).

In conclusion one more important point should be emphasized. While all so-called irritant diuretics, spices, ethereal oils, cantharides, metallic salts, and even concentrated salt solutions, when administered subcutaneously damage the kidney and cause albuminuria, the drugs of the caffeine group cause no pathological alterations in the kidney, even when they are administered repeatedly in large or even in poisonous doses. They may, therefore, be administered during long periods, and even in the presence of parenchymatous nephritis, with less risk than any other diuretics. It is even possible that the improved blood flow to the kidney may exert a beneficial effect on the diseased organ (*Loewi*).

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EFFECTS OF THE DIGITALIS SUBSTANCES ON THE RENAL BLOOD FLOW

The members of the digitalis group resemble the purine bodies in one particular,—that is, in their power actively to dilate the renal vessels.

While it is well known that the most important therapeutic property of this group is their power of improving a pathologically weakened heart function and in this way increasing diuresis indirectly by improving the general circulation, it was emphasized by *Lauder-Brunton* and *Power,* as early as 1874, that digitalis may act as a diuretic even in normal men in whom the heart function is an optimal one. It may also be shown, as has recently been done by *Loewi* and *Jonescu,* that increased diuresis occurs in the normal healthy animal after digitalis and especially after doses so small as to cause no rise in the blood-pressure. Under these conditions the oncometer shows that there is a marked increase in the volume of the kidney, indicating dilatation of the vessels and increased flow of blood through it. In accordance with this is the fact, long known by clinicians, that digitalis increases the diuresis in cardiac patients and causes a disappearance of œdema, usually without increasing the blood-pressure, and often in fact when the pulse is markedly slowed and the pressure in the large arteries decidedly diminished.

This action of digitalis on the renal vessels is a purely local one, for it also occurs in a kidney which has been deprived of its nerves. In this particular digitalis acts in the same way as caffeine and its congeners. As, however, digitalis does not appear to exert the second diuresis-producing action of caffeine, the inhibition of reabsorption, its direct diuretic effect is only slight as compared with that of caffeine.

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3. SECRETION AND REABSORPTION IN THE TUBULES

Whether or not it is possible by the use of pharmacological agents to cause or to increase the excretion of water by the tubular epithelium is not known with certainty (*Frey*).

The limitation of the reabsorption of water in the tubules, which may be considered as analogous to diarrhœa in the intestines, has been shown to be one of the factors in the action of the diuretic salts as well as that of caffeine. As an unmixed diuretic action it occurs in phloridzin diabetes.

Phloridzin Diuresis.—Phloridzin is a glucoside but slightly soluble in cold water, readily soluble in alkalies and in alcohol, that occurs in the roots of apple, cherry, and plum trees. *v. Mering* discovered that internal administration and, even better, the subcutaneous injection of small amounts of phloridzin, caused a pronounced glycosuria, which, as has been shown by later experiments, is due to the formation and excretion of glucose in the kidney. The sugar after being excreted into the tubules hinders the reabsorption of water by its osmotic power,—that is to say, by its power of attracting and holding water (*Loewi, Loewi u. Neubauer*).

If the kidney be diseased, the glycosuria occurs more tardily and weakly or not at all. This has led to an attempt to use the glycosuria reaction to this drug for the functional diagnosis of the kidney (*Kapsammer*). The dose administered hypodermically in such cases is 0.01 gm. in alkaline or dilute alcoholic solution.

In diabetes insipidus the indication is to limit the excretion of urine, some cases excreting very large quantities (up to 10 l. or more) of very dilute urine, which causes a constant thirst and forces the patient to consume correspondingly large quantities of water. The cause of this disease in many cases is a disturbance in the central nervous system, presumably a chronic excitation of the vasodilator nerves. In accordance with such assumption, large doses of narcotics, opiates, valerian, etc., at times favorably influence the condition, at least temporarily. [Strychnine is also apparently at times of value in the treatment of this condition. It is possible that the good results following its administration may be due to a centrally excited constriction of the renal vessels.—Tr.]

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INFLUENCE OF GENERAL AND RENAL METABOLISM ON THE COMPOSITION OF THE URINE

It is evident that the chemical composition of the urine will depend on the metabolic processes, on the diet, and also on foreign

substances, taken intentionally or otherwise, which are excreted in the urine in altered or unaltered form or combination. Ever since the investigations of *Schmiedeberg* dealing with the formation of hippuric acid in the kidney, it has been known that the kidney itself is capable of both synthetic and catabolic activity and in such fashion plays a rôle in determining the composition of the urine.

URINARY ANTISEPTICS

The power which the renal parenchyma possesses of splitting up substances into simpler components is possibly of much significance for the action of some of the urinary antiseptics. These are substances which, when introduced into the body, become active chiefly or only after being split up in the kidney. In this group belong, among others, *uva ursi,* which is used as an infusion or fluid extract in the treatment of cystitis. It contains, in addition to some tannin, the glucoside arbutin, which is split up in the kidney into sugar and the antiseptic hydrochinone (see p. 514). **Salol,** much used as a urinary antiseptic, may possibly owe its activity to a similar decomposition, and possibly the same is true of the ethereal oils of **copaiba, sandal-wood,** and **cubebs.** In the metabolism these are combined with acids, with the formation of the inactive ethereal sulphates and glycuronates, which possibly are again changed into the active form by decomposition taking place in the kidney. According to *Jordan,* the oil of sandal-wood exerts a powerful effect, particularly in staphylococcus infections.

Formaldehyde Derivatives.—However, all the urinary antiseptics thus far mentioned are far less effective than *hexamethylenamine* (*urotropine*) and some closely related substances, such as *helmatose* or *new urotropine,* which is hydromethylencitrate of urotropine, and *hippol,* which is methylenhippuric acid, and others. The activity of these substances depends on the fact that formaldehyde is split off from them (*Jordan*).

Hexamethylenamine.—The decomposition of hexamethylenamine occurs but slowly under the influence of a neutral reaction, much more rapidly in an acid medium, and not at all in an alkaline one. Its efficiency is therefore lessened by the simultaneous administration of alkalies, and favored when acids, such as acid phosphates, are administered. The urine in cystitis, as a rule, does not become alkaline until it is decomposed by bacteria in the bladder, and is usually acid when it leaves the kidney, so that there formaldehyde can be formed from the hexamethylenamine. *Hippol, on the other hand, is more readily decomposed in the presence of an alkaline reaction.* These preparations, hexamethylenamine or hippol, in a dosage of 0.5–1.0 gm., 4–6 i. d., will prevent with reasonable certainty, ammoniacal fermentation and the formation of phosphatic concretions occasioned by it. Other urinary

infections are affected by them in varying degree according to the resistance of the infecting organisms. The typhoid bacilli seem to be more readily overcome than any others (*R. Stern*).

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Alkalization of Urine.—Acid urine may be readily rendered alkaline by the administration of alkaline salts or the salts of the vegetable acids, or simply by a diet consisting chiefly of vegetables and fruits. By such measures it is possible to cause an excretion of the alkaline carbonates in the urine which will neutralize the acids normally present. Such measures, as a rule, increase the ion concentration of the urine. In case it is wished that the urine be rendered alkaline without at the same time becoming more concentrated, such alkalies as magnesia, calcium carbonate, etc., should be administered. These are not absorbed, but neutralize the acids in the intestine and deprive the urine of a portion of its acid constituents. Such effects appear to be of value when the indication is to bring about the solution of uratic concretions in the kidney and bladder. The recognized value of the waters containing the alkaline earths in the treatment of the uric acid diathesis depends on such action.

Atophan.—The excretion of uric acid by the kidney is not appreciably affected by alkalies, but phenylchinolincarbonic acid, $C_{16}H_{11}NO_2$, atophan, in doses of 2 to 3 gm. daily, very markedly increases the excretion of this substance in a way which is not yet understood. As a result of the increased removal of the urates from the blood, the deposits of the urates in the joints and elsewhere pass into solution, and the symptoms due to them are relieved. (*Weintraud,* also consult p. 421.)

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CHAPTER XI

PHARMACOLOGY OF THE SECRETION OF SWEAT

PHYSIOLOGY

Composition.—The sweat, containing from 97.5 to 99.5 per cent. of water, contains less solid matter than any other secretion of the body (*Harnack*). Excluding foreign admixtures from the sebaceous glands, almost three-quarters of its solids, which amount to 0.5–2.5 per cent., are inorganic salts, chiefly NaCl, only traces of phosphates and sulphates being present (*Kast*). Urea makes up more than one-half of the organic constituents, which otherwise consist of urates, creatin, aromatic acids, ethereal sulphates, and other nitrogenous metabolic products which are excreted in the sweat.

Under average conditions of intake and output of water, amounting to about 3 litres per diem, the loss by sweating amounts to about 40 c.c. per kilo of body weight every hour, which for 24 hours amounts to about 700 c.c. for an average weight of 70 kilos (*Schwenkenbecher*). These figures hold, however, only during rest and with moderate external temperatures, for under other by no means unusual conditions the loss of water through the skin may be greatly increased.

Cramer estimates, from the amounts of sodium chloride on the surface of the skin, 814 c.c. during exercise out of doors, and 3208 c.c. for 24 hours during marching in summer heat. Sweat baths and similar procedures cause much more rapid sweat secretion, for example, ½–1 litre in a half hour (*Strauss*), but this naturally only for comparatively short periods. The enormous number of the sweat-glands in some situations, 500–1900 to each square centimetre of skin, explains their great efficiency.

As the estimation of the NaCl on the surface of the skin has shown that sweat secretion in man continues under all external conditions of temperature (*Cramer*), although only in almost imperceptible amounts during cold weather, it is improbable that water vapor passes through the epidermis as a result of purely physical processes and without the aid of the sweat-glands (*Schwenkenbecher*).

Excretion of Nitrogen and Salts.—In spite of their low concentration in the sweat, the absolute amounts of urea and salts thus lost by the body are not to be disregarded, even under normal conditions, *Cramer* finding 3.7 gm. NaCl and up to 1.0 gm. N excreted by the skin in 24 hours under conditions of moderate exercise in the summer, while during hard work in high temperatures the sweat secreted may contain as much as 12 per cent. of the total N excreted. With patients at rest and with mean external temperatures 0.3 gm. NaCl and about the same amount of nitrogen represent average figures, which are increased by thorough sweating up to 1.0 gm. of each in 24 hours (*Schwenkenbecher u. Spetta*). The concentration of sweat is increased during active perspiration, but when this becomes

really profuse the concentration falls below normal. Still, with impaired renal secretion (anuria in cholera, uræmia, etc.) salts and urea may be excreted in the sweat in such quantities that crystals of NaCl or clusters of urea crystals have actually been found on the skin.

Human sweat is usually acid in its reaction, the acidity being probably due entirely to the fatty acids from the sebaceous glands, but when sweating is artificially stimulated it quickly becomes alkaline like that of the lower animals (*Trümpy, Camerer*).

The sweat-glands therefore are to be considered as excretory organs for water and salts and also for nitrogenous metabolic products. Under normal conditions, however, their chief function is that of regulating the body temperature, by providing for the excretion and evaporation of water on its surface (see Pharmacology of Heat Regulation).

These glands are very differently developed in different animals and also in different parts of the body. In man the whole skin perspires, certain portions of the face, the palms of the hand, and the soles of the feet being especially richly supplied with sweat-glands; but in cats and dogs visible perspiration occurs only in the hairless soles of the feet, although sweat-glands do exist in other portions of the skin. Rats, mice, and rabbits do not sweat at all, while it is well known that horses sweat over the entire skin.

The secretion of sweat is a true glandular activity,—that is, it, unlike that of urine, results from excitation of secretory nerves and is relatively independent of the blood-pressure and blood flow, active sweating occurring often in conditions in which the skin is very poorly supplied with blood (cold sweat, death sweat, etc.), although, generally speaking, the secretion is freer when the blood supply is ample.

Luchsinger, by showing that stimulation of the sciatic excited free sweat secretion after ligature of an artery or constriction of a limb, or even 20 minutes after amputation, clearly demonstrated that this secretion is independent of the blood supply (*Kendall, M. Levy*).

Innervation.—The secretory nerves of the sweat-glands belong exclusively to the sympathetic nervous system (*Langley*).

Those for the hind legs of the cat leave the cord partly with the twelfth and thirteenth dorsal, but chiefly with the first and second lumbar nerves, while those for the forelegs pass out with the fourth to ninth dorsal nerves. They all pass through the sympathetic trunk and via the sciatic nerve and the brachial plexuses respectively to the balls of the feet. The spinal centres consequently no longer control sweat secretion in the hind legs after section of the sciatic or of the sympathetic trunk above the sixth lumbar ganglion.

The spinal sweat centres are primarily under the control of the thermoregulatory centres in the midbrain, but may also be influenced by other parts of the central nervous system, and may be stimulated by most various sensory stimuli, which often produce sweating only in

certain limited portions, as, for example, the localized sweating above constantly active muscles. The sweating during nausea and that due to stimulation of the cerebral cortex from anxiety or fear are well-known examples of the effect of the stimulation of the sweat centres associated with stimulation of higher portions of the central nervous system (*Winkler*).

Heat is the most important physiological stimulus for this excretion, it exciting these centres through the mediation of higher centres which control the regulation of the body temperature (see this chapter) and send impulses down to them. *Kahn* has shown that warming the blood flowing to the head without warming the rest of the body brings about a dilatation of the cutaneous vessels and strongly excites the secretion of sweat, thus demonstrating that the mechanism for loss of heat by sweating is started working by the action of the higher centres on centres in the cord.

Sweating is excited both by interference with heat loss and by increase of heat production—for example, by active muscular exertion—and also by external heat. In the usually employed sweating procedures the attempt is made both to prevent heat loss, by such measures as warm covering and packs, and to introduce heat from without, as by drinking hot fluids, such as tea or other warm drinks.

Sweating is also favored by heat applied locally to the secretory nerve-endings, for these respond to stimulation more actively if the skin be warm than when it is cold (*Schierbeck*); in fact, cooling of an extremity can entirely prevent any response to stimulation (*Kendall, Langley*).

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DIAPHORETIC DRUGS

If in fever the cutaneous vessels are contracted, the attempt is often made to overcome this by **alcohol**, which is administered in the form of hot diluted alcoholic drinks, with the object of dilating the cutaneous vessels in order that an ample blood flow in the skin may favor a free perspiration.

DRUGS ACTING CENTRALLY

The secretion of sweat may also be excited by drugs acting on the sweat centres as well as by those acting in the periphery. As anything which stimulates the spinal centres also stimulates the sweat centres, strychnine, camphor, picrotoxine, and ammonium salts excite sweat secretion in cats, but this effect is not produced after division of the sciatics (*Luchsinger, Marmè, Nawrotzi*). Camphor and the liquor ammonii acetatis were formerly much used as sudorifics.

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DRUGS ACTING ON THE PERIPHERY

The sympathetic nerve-endings in the glands are acted upon by a number of drugs which elsewhere act only on autonomic nerve-endings, while epinephrin, which elsewhere acts specifically on the sympathetic system, has no effect on the sweat-glands, in contradistinction to its effect on the glands in the skin of the frog. On the other hand, muscarine, pilocarpine, and physostigmine all excite, while atropine suppresses, the secretion of sweat. Although the innervation of the sweat-gland is, as far as is known, purely sympathetic, in their pharmacological reactions, their insusceptibility to epinephrin and their susceptibility to the autonomic drugs, they behave entirely like organs with autonomic innervation. No explanation has thus far been found for this striking exception to otherwise apparently general laws.

Luchsinger long ago demonstrated that muscarine, pilocarpine, physostigmine, and atropine act peripherally in the sweat-glands. Pilocarpine especially has a strong sudorific effect in the cat's paw, even after section of the sciatic; in fact, at first it acts more strongly on the side where the nerve has been cut than on the other side, and the same is true of muscarine (*Trümpy*), but, according to *Luchsinger*, the intravenous injection of physostigmine produces no effects on the sweat-glands after they have been cut off from their nervous centres. Under these conditions it excites secretion only when injected under the skin of the paw. These observations are in no way surprising in view of the pharmacological characteristics of this drug (see p. 148), for, while everywhere markedly increasing the excitability of nerve-endings, it, in contradistinction to muscarine and pilocarpine, does not itself act as a direct stimulus.

It is entirely in agreement with the fact that these drugs act peripherally that after an injection of pilocarpine the general sweating is preceded by a strictly localized perspiration (*Cloetta*), which after very small doses may be all that occurs (*Strauss*), and that, on the other hand, small doses of atropine given hypodermically may produce only a local suppression of perspiration.

Arecoline, the alkaloid of the areca nut, and nigelline, from the seeds of Nigella sativa (*Pellacani*), act like pilocarpine, but are of no practical significance.

In the sweat-glands, as in the salivary glands, pilocarpine and atropine are reciprocally antagonistic; but the affinity between atropine and the nerve-endings is so much the stronger, that pilocarpine can start up the sweat secretions again only in case the dose of atropine has not been too large, while atropine is able to counteract even the strongest pilocarpine action (*Luchsinger*).

The action of **nicotine** on the secretory nerves of the sweat-glands accords fully with other experiences bearing on the action of this drug on the relay stations (ganglia) in the vegetative nervous system. *Luchsinger* found that after section of the sciatic it was either not at all or only very slightly active. According to *Langley*, the ganglia of the sudoriparous fibres lie in the sympathetic trunk, which arrangement accords with the fact that the primarily exciting action of nicotine is localized at this point.

Central Actions of These Drugs.—Pilocarpine, physostigmine, and nicotine also stimulate the spinal sweat centres, as shown by *Luchsinger*, who found these drugs, when injected into the back, produced sweating in the extremities even after the arteries supplying them had been ligated. This central action of these drugs is to be considered as analogous to that of other central excitants, such as camphor, picrotoxin, and many others, for all three at first cause an excitation of the cord, which manifests itself by dyspnœa and after toxic doses by convulsions, and which after pilocarpine is especially lasting but with nicotine soon passes over into paralysis (*Harnack u. H. Meyer*). It is readily comprehensible that augmentation of the impulses from the centres will be especially effective in combination with the simultaneous excitation of the terminal nervous organs. This is especially so with physostigmine, whose peripheral action is solely to increase the excitability of the terminal nervous organs.

In therapeutics of the substances mentioned only pilocarpine is of importance as a diaphoretic or hidrotic, while atropine is the most important antihidrotic.

Pilocarpine is derived from the jaborandi leaves obtained from different pilocarpus plants, and is accompanied in the leaves of Pilocarpus jaborandi by a second alkaloid with similar but very much weaker actions (*Harnack*). The leaves were introduced from Brazil in the seventies, but they have been found to be unreliable and uncertain in their actions, perhaps on account of the presence in them of jaborin, a decomposition product of pilocarpine of basic nature and atropine-like action, which may also be present in impure pilocarpine. The use of the leaves has therefore been abandoned, and properly so.

The hydrochlorate of pilocarpine is the preparation to be used, and it is usually administered hypodermically in doses of 0.005–0.01 gm. (maximum, for single dose 0.02 gm. (!! Tr.), per diem 0.04 gm.)

Usually ten or fifteen minutes after an injection the skin becomes reddened and very profuse sweating occurs, lasting about two hours, during which time as much as 2 kilos of fluid may be secreted. An increase of salivary secretion almost always accompanies or precedes the sweating and persists somewhat longer. The salivary secretion usually is not increased to a disturbing extent, but occasionally the effect on the salivary glands exceeds that on the sweat-glands or it alone may occur. The secretions of all other true glands are also increased, among them those of the lachrymal, bronchial, and tracheal

glands. The effect on the bronchial glands is of practical importance, inasmuch as it may increase the danger of œdema of the lungs in individuals already predisposed thereto. *This drug produces no demonstrable effects on the renal or lacteal secretions.*

Other Actions.—While an increase in the various secretions may be induced by muscarine or nicotine only simultaneously with other dangerous symptoms, after pilocarpine this is usually the first effect produced, and occurs after such small doses that there is no danger to be apprehended from its actions on the various autonomic nerve-endings. In its actions on these it closely resembles muscarine and nicotine. Its effects on the eye (p. 153), on the intestine (p. 190), and on the uterus (p. 222) are analogous to those of muscarine, while its action on the heart is identical with that of nicotine. These side actions are often disagreeable and disturbing when pilocarpine is administered medicinally. Especially visual disturbances and nausea and vomiting may result from its administration, but colic and diarrhœa occur only rarely. As even therapeutic doses excite uterine contractions, this drug should not be administered to pregnant women [except in the presence of the clearest indications.—Tr.].

At the start pilocarpine produces excitation of the central nervous system. In animal experiments the paralysis of the vasomotor and respiratory centres results only from much larger doses than those which cause an increased secretion of sweat. Still the collapse which not infrequently has been observed in man, when larger doses of pilocarpine have been given, may be a result of this central paralysis. It is therefore contraindicated to use pilocarpine in doses larger than 0.01 gm.!

According to *Eichelberg*, pilocarpine causes an increase in metabolism during the active glandular activity caused by it. In the fasting animal the increase of the CO_2 excretion during the period of secretion amounts to only about 9 per cent. (*Frank u. Voit*). It is therefore not very marked, but may well be of some importance in causing the wasting which may occur when sweating cures are employed (*Schwenkenbecher u. Inagaki*).

Other Diaphoretics.—In addition to pilocarpine, only the *salicylates* and other *antipyretics* are of much importance as diaphoretics. These produce their diaphoretic action by their effect on the regulation of the body temperature, by acting on those higher centres which control the spinal sweat centres (see p. 370).

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INDICATIONS FOR DIAPHORESIS

Diaphoresis may be employed for the purpose of removing water from the body or to bring about an excretion through the skin of substances ordinarily excreted by the kidney. In addition to these scientifically well-grounded indications, diaphoresis is frequently employed empirically to meet various others,—as, for example, in the beginning of infectious diseases, with the idea of securing the elimination of bacterial toxins, or in a number of mild febrile affections, such as bronchitis, etc., to "bring them to the surface." It is probable that the experience, that in many infectious diseases improvement often starts simultaneously with the appearance of profuse sweating, has led to the belief that the improvement in the patients is due to this.

In Renal Disease.—On the other hand, the excitation of profuse diaphoresis is of proven value in acute or chronic renal insufficiency, as the vicarious secretion through the skin, which in the course of a thorough sweating may remove large amounts of water, urea, NaCl, etc., from the body, helps to relieve the kidney.

It is no unusual clinical experience to see, in cases with insufficient or suppressed renal secretion and impending uræmia, an improved diuresis follow a thorough sweating, and this, too, independently of the mechanical relief secured,—such, for example, as relief of the compression of the renal veins by ascites. This reminds one of the fact mentioned on page 356, that an excess of salts in the blood may cause a lessening of the renal secretion, which may be relieved by withdrawing salt from the diet. The removal of salt from the body by sweating may have a similar favorable effect.

Sweating may also be employed as a measure of last resort to remove fluid in dropsical conditions, but in connection with the use of pilocarpine in cardiac patients it is important to remember that this drug may cause collapse.

The effects produced by pilocarpine when employed as an "absorbant," for the purpose of aiding in the absorption of exudates or of extravasations of blood in the anterior chamber of the eye or of cloudiness in the vitreous humor, probably depend on the temporarily increased concentration of the blood which may result from sweating, even when the water content of the tissues is so low that diuretics fail to act.

SUPPRESSION OF THE SECRETION OF SWEAT

Atropine in doses of 0.5–1.0 mg., usually given hypodermically [? Tr.], may be employed with advantage for the purpose of suppressing profuse sweating, such as the "night-sweats" of consump-

tives. As the very first expression of the action of atropine is the inhibition of various glandular secretions, such doses may accomplish this without necessarily causing any other atropine effects except some dryness of the mouth and throat, but if the dose be increased or often repeated the other atropine effects may prove very disturbing.

Agaricin.—Agaricinic acid, which is obtained from the white agaric (Polyporus officinalis), long known to possess antihidrotic properties, acts on the secretory nerve-endings like atrophine. This is the active substance contained in the impure commercial preparation known as agaricin, which is often used in the treatment of the night sweats of phthisis (0.005–0.01 gm. for single doses, 0.1 gm. maximum dose for 24 hours). It has been shown by *Hofmeister* that this substance, which in large doses acts as a narcotic but which otherwise is not pharmacologically related to atropine, exerts a weak, atropine-like action on the sweat secretion and does this in relatively non-toxic doses. Under its influence sweating does not occur as it usually does when a cat's paw is kept warm. This effect is peripherally induced, for after agaricin stimulation of the sciatic is ineffective. On account of its local irritant action, agaricin cannot be administered hypodermically.

Camphoric acid, obtained by the oxidation of camphor, in doses of 1–2 gm. is also employed to prevent night-sweats, but no experimental investigations of its efficiency have been made (*Vejux Tyrode*).

Astringents, such as tannic acid and astringent antiseptics, may be useful in relieving local hyperhidrosis.

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CHAPTER XII

PHARMACOLOGY OF THE METABOLISM

GENERAL CONSIDERATIONS

In the living body there is a constant change taking place in the forces and substances which form and maintain it. The organism is able to maintain itself and keep its weight and chemical composition constant, except for occasional variations, only by periodically absorbing and assimilating material to replace that constantly lost by disintegration and death of its tissues, for living matter is constantly dying. We speak, therefore, of metabolic balance and equilibrium and of positive and negative metabolic balance, depending on whether or not assimilative or dissimilative phenomena are preponderant. All the chemical substances constituting the body take part in the tissue change, the inorganic mineral constituents which largely constitute the framework of the body taking the least active part in these changes, but still taking some part therein. Therefore all the constituents of the body must be constantly replaced to some extent if the organism is to survive (law of the minimum). Naturally the most active metabolism is that of the readily oxidized organic substances, of which the proteids, fats, and carbohydrates are the most important, for these, on account of their oxidizability, are at once the creators and the victims of the chemical energy, which enters the body with them only to leave it almost entirely in the form of heat and work.

The chemical processes of oxidation and decomposition are in theory of two types:

1. Decay of protoplasm as the result of the naturally limited life of all cells, the tissue change of death or of wear and tear, which takes place without regard to the energy which thus unavoidably becomes available. This is especially apparent in the decay of the epithelium of the skin and similar tissues and in that of the nuclear constituents, both of which are, from a caloric point of view, of minor significance.

2. Decomposition of the replaceable constituents of the protoplasm for the purpose of supplying the energy (heat and force) necessary to life. This is functional tissue change, or metabolism of work, which occurs without combustion of the formed elements. In general this corresponds to the metabolism of nutrition, it being, in other words, the combined result of dissimilation or catabolic (splitting) processes and of assimilation or anabolic (synthetic) processes in the cells of the body, and is in rapidity and extent by far the more important type of tissue change.

The total metabolism, therefore, renders possible the transformation of energy in the body, which may be measured directly by

determining the caloric intake and output or indirectly by determining the consumption of oxygen and the output of carbon dioxide. (For methods, *Magnus-Levy, Durig.*)

The amount of the energy transformed varies within wide limits, being governed by external and internal conditions influencing the organism and by the work performed. A certain minimum is, however, necessary to maintain the body temperature, the heart's action, respiration, etc., and, if the functional metabolism cannot supply this, the tissues themselves are consumed. A sharp distinction can, however, not be drawn between these two sources of supply, for reserve material is stored up in the different organs, which, in case of insufficient nutrition, is rendered available for oxidation, and in the following order, first carbohydrates, second fats, and last of all proteids. Only when this reserve supply has been consumed does a rapid destruction of cells begin.

The measurement of the energy transformed furnishes a general gauge for the momentary tissue change, but gives no indication of the manner or extent to which each of the three main food-stuffs, proteids, carbohydrates, and fats, take part in this process. With the total transformation of energy remaining constant, it is possible for these three mainstays of metabolism to be involved in very different proportions, for they can, within certain limits, replace one another in accordance with their caloric values, an abnormally increased or diminished decomposition and oxidation of one constituent of the body being compensated for by the opposite behavior of the others. As here it is a question of equivalent quantities, not in terms of mass but in those of caloric values (according to *Rubner* in round figures 100 gm. fat = 230 gm. glycogen = 230 gm. dried muscle proteid or 980 gm. lean meat), the body may gain or lose in the mass of its organic constituents, while a constant amount of energy is transformed, according as it retains or consumes larger amounts of carbohydrate or smaller amounts of fat, which are, however, calorically equivalent. On the other hand, the mass of material,—*i.e.,* the body weight—may remain constant and energy be lost if, for example, 100 gm. of fat be consumed and 100 gm. of carbohydrate be assimilated. Determinations of the energy transformed consequently can indicate only the extent of tissue change, but cannot show whether the tissue balance is positive or negative. The much-used expression, "stimulation of metabolism," is therefore in no sense an exact one, for it may signify—and this is the usual meaning in therapeutic literature:

1. An increased transformation of energy,—*i.e.,* increased heat production and increased functional activity of the organs, resulting in an increase in the intensity and speed of all the phenomena of life and of decay. In other words, it may mean that in a given time more oxidizable material is consumed without considering for the time any change in the energy balance. If one assumes with *Rubner* that each and every cell protoplasm during its life is capable of

transforming a certain amount of energy, and that, after performing a given amount of work, it is used up and disintegrates, it is evident that a therapeutic acceleration of the transformation of energy will bring about a more rapid dying off of cells already feeble from old age or otherwise pathologically weakened, and that thus the new growth of the healthy younger generation replacing them may be accelerated. In this fashion purification and regeneration may be brought about and the useless elements be removed from the body. The utility of all those therapeutic agencies, which in an indirect fashion tend to increase the transformation of energy, probably depends on their power of inducing such regeneration. Among such measures stimulation of the skin, sea-bathing, climate,* sports, and massage may be mentioned. In so far as they facilitate or stimulate muscular activity, the stimulants of the central nervous system may be considered as doing this. Among these are strychnine, caffeine, alcohol in small amounts,—in short, all those drugs known as "excitantia nervina," or nerve stimulants.

Disappearance of Pathological Tissue as a Result of General Acceleration of the Transformation of Energy.—Such a regenerative selection—that is, an extermination of less resistant, degenerated, or otherwise weakened body cells—may be accomplished by chemical or physical forces, which, while reaching all or most cells in equal intensity, exert on them an action supported without apparent damage by healthy cells, but fatal to unhealthy ones. This may be compared to the way in which it is possible by the application of such mild caustics as lactic acid to destroy diseased tissue without harming the healthy tissue necessarily submitted to the same treatment. Of the agencies acting in this fashion the physicochemical ones, heat and radiant energy, may be considered as having such effects, though only to a limited extent. Variations in the osmotic tension of the tissue cells—that is, in their water and their salt content—produce such effects to a marked extent. This is the basis for the various popular blood-purifying cures, water cures, thirst cures, and so forth.

Specific Alteration of Metabolism.—While an alteration of osmotic conditions affects all the cells of the body as a whole, and by physicochemical "mass action" disturbs the chemical equilibrium of all of them, considered as elementary organisms, and alters their function, there are also purely chemical agents, which in a more delicate manner, that is not susceptible of a further analysis, accelerate or retard only certain of the chemical reactions of protoplasm, without otherwise altering its structure or function. These may be looked upon as specific catalyzers of the metabolic processes, to which we reckon the products of certain glands, especially that of the thyroid and, in a limited and opposite way, quinine.

2. Stimulation of the metabolism indicates quite another thing when the object is to secure an *increased assimilation of material,*

* See *Loewy u. Fr. Müller.*

whether this means a more rapid and greater increase of weight in young, rapidly growing individuals or the attainments of a better state of nutrition in badly nourished adults, such as invalids or convalescents. Here the indication is not to accelerate the transformation of energy by increasing catabolic processes, such as oxidation and cleavage, but rather to moderate it as far as possible or to overcompensate for it. As a matter of fact, in such cases the transformation of energy is, as a rule, augmented, while proteid is assimilated and retained as organ proteid. In addition to purely dietetic measures and those which improve the appetite and the digestion and absorption, such as forced feeding, with exercise, a number of pharmacological agents may produce these effects by specifically influencing tissue change in such fashion that assimilation—that is, the synthetic formation of new body substance—is stimulated, and a condition results similar to that of the youthful growing organism (*Hoffstrom*) or to that of an individual convalescing from an exhausting disease (*Lüthje u. Berger*). Of the manner in which such effects are produced little is known up to the present.

When the action is more pronounced or when toxic doses are given, these same substances act harmfully on the protoplasm of the cells, causing their rapid death and accelerating their disintegration. Under certain conditions both the favorable and the destructive actions may occur simultaneously in the body as a result of the variable resisting powers of the cells of the body. This may explain many specific curative actions.

Furthermore, such actions on metabolism, partly conservative and partly harmful, may be so feeble or may be limited to such small especially susceptible portions of the body that they cause no observable effects on the general metabolism and therefore cannot be measured. However, clinical observation of resulting changes in the distribution of material in the body, such as the absorption of exudates, tumors, or connective-tissue growths, can give sufficient evidence to permit the assumption of such actions on the metabolism. The substances producing such results will be considered later in the group of inhibitors of oxidation (p. 404).

3. Finally, AN ALTERATION OF METABOLISM may be considered, WHICH AFFECTS CHIEFLY OR ENTIRELY ONLY CERTAIN CONSTITUENTS OR DECOMPOSITION PRODUCTS OF THE PROTOPLASM of the body. This therefore demands a special discussion.*

* This general discussion and division under 1, 2, and 3 are schematic and to a certain extent arbitrary, for they include only some of the pharmacologically interesting phases of metabolism.

In physiology it is customary to differentiate between the tissue change necessary for maintenance of metabolism during rest, *i.e.*, the energy transformation occurring in a fasting human being during complete inactivity, and the augmentation of metabolism resulting from definite work performed by the organs—functional metabolism. The metabolism during rest, however, in addition to the

In so far as the function of the cells is under central nervous control, it is clear that their metabolism also may be indirectly influenced through the central nervous system, for every functional act, every cell activity, depends on a catabolic change, which is quickly followed by a compensating—often, in fact, by an over-compensating —restorative process. This reaction resulting in compensation or over-compensation is one which we are not yet able to analyze or understand. Like the capacity for growth, it is an essential characteristic of living matter.

The stimulation of growth, with assimilation of proteid, which continued and violent muscular exercise causes is the best example of such over-compensation (*Caspari, Loewy, Bornstein*). The increased blood and food supply brought to the organ as a result of its functional activity doubtless is a factor, but only a partial factor, in this result. On the other hand, organs forced to remain inactive undergo atrophy.

The chemical regulation of the body temperature (see Chapter XV) is another instance of a metabolic process controlled by the nervous system, which demands special separate consideration.

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Aside from these indirect influences through the central nervous system, all physical or chemical stimuli which act directly on the cells of the body must influence their chemical activity, and thus affect the transformation of matter and energy in them. For reasons of practical import, it is advantageous to start the discussion of such direct influences with that of—

purely vegetative metabolism of decay, includes a large portion of the functional metabolism, as it necessarily includes the metabolism resulting from the activity of the heart, of the respiratory system, and of the glands, as well as that involved in the production of heat. These two components, however, are influenced by pharmacological agents in very different degrees and in opposite directions. Drugs which, like arsenic, influence the metabolism of decay, affecting the duration of the life of the cells, do not necessarily produce an appreciable alteration in the metabolism of function. On the other hand, drugs affecting function, such as the narcotics, or those acting on nerves or on the heart, etc., as a general rule do not affect the metabolism of decay, although they primarily increase or decrease the transformation of energy and material, the functional metabolism, only of the organs whose activity is stimulated or depressed. For these reasons the appreciation of the difference between metabolism of decay and metabolism of function appears essential to the proper understanding of the manner in which drugs produce alterations in the metabolism.

1. THE TEMPERATURE OF THE BODY

It is well known that an increase in the temperature causes an acceleration of the rate at which all chemical reactions take place. According to *van't Hoff,* a rise of 10° C. almost doubles or trebles the rate of reaction. Within certain limits of temperature the same holds good for biological phenomena (*Linser* and *Schmid, Matthes, Kanitz*), every rise in the body temperature beyond the normal increasing and accelerating the metabolism, while marked lowering of the body temperature retards and lessens the metabolism (*Rumpff*).

Such overheating or cooling of the body may indirectly result from the action of drugs which, like cocaine, tetrahydronaphthylamine, and atropine, excite the centres controlling the heat regulation, or which, like the narcotics, especially alcohol and chloral and the antipyretics, depress them. (See *Loewi* and also Chapter XV.)

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2. LIGHT AND RADIANT ENERGY

Natural illumination indirectly exerts an influence on the metabolism, inasmuch as through the eye it constantly sends sensory impulses to the central nervous system, as a result of which, muscular tension and movements are excited and possibly also other vital processes,—for example, the formation of the red blood-cells (*Marti u. Kronecker*).

As far as has been proven, however, only the *blue-violet* and *ultra-violet rays* exert a direct influence on the chemism of the cells of the higher animals. These rays exert a destructive action on enzymes and on living protoplasm, just as they do on all chemically labile substances. This power is systematically employed in phototherapy, in the treatment of lupus, cancer, etc., according to such methods as that of *Finsen,* and by means of especially adapted sources of light.

Of a similar nature is the action of the luminous energy absorbed by fluorescent substances. Such substances as quinine, eosine, acridine, etc., when charged with this energy, as long as they remain exposed to light decompose living protoplasm and other very susceptible substances, such as enzymes, toxalbumins, etc. According to *v. Tappeiner* and *Jodlbauer* and to *Straub,* ionized oxygen is probably the active agent in this destructive action. In therapeutics this property of these substances may be utilized by such methods as painting 0.1–0.5 per cent. eosin solution on those portions of the surface of the body where a corrosive effect is desired and exposing them to sunlight.

As a result of their absorption by fluorescent substances, the yellow and red light waves, which ordinarily are inert chemically, may

be rendered chemically active, and, as these rays penetrate vegetable and animal tissues more readily than the violet ones, it is perhaps possible for them to produce effects in the interior of the body if the tissues are impregnated with yellow or red fluorescent substances.

Hæmatoporphyrin, a hæmoglobin derivative almost constantly found in human urine, is markedly fluorescent, and under the influence of light exerts marked hæmolytic actions. It is probably constantly present in the mammalian organism, although normally the amount present is extremely small. If abnormal amounts of it appear in the blood, those portions of the skin which are exposed to the sun may become diseased. This is probably the cause of the skin lesions in hydroa æstiva (*Hausmann*). It also appears probable [? Tr.] that a photodynamic substance present in the corn consumed is of significance in connection with the skin lesions of pellagra (*Horbaczewski, Raubitschek, Hausmann*).

Röntgen Rays and Radium Emanations.—Finally, mention should be made here of the similarly destructive action of X-rays and of radium emanations. On account of their power of penetrating the soft parts of the body, their action is not confined to the surface, but also affects the blood and tissues in the interior of the body. Exposure to them results in a destruction of the red cells and accumulation of pigment in the body, and more especially in a very extensive destruction of myelocytes and lymphocytes and of lymphoid tissue. This latter action has been utilized in the treatment of leukæmia. Other cells also of embryonal type, such as the germinal cells of the sexual organs and the cells of pathological new growths, are readily affected and destroyed. This destruction of cells results in an increased decomposition of proteid and increased excretion of nitrogen.

Radio-active Waters.—Radio-active minerals and earths, such as the uranium slag from the mines of Joachimsthal, when placed in water, give off radio-active emanations to it. Consequently the waters of many springs are naturally radio-active, while ordinary water may be made so by being kept for many hours in contact with radio-active material.

Although it is highly probable that the radio-activity of baths and drinking waters can exert an influence on the human organism, this cannot be asserted positively. Clinical experience, however, has led to the belief that radio-active waters exert a beneficial action on rheumatic and other similar conditions. It has been possible to cause a disappearance of uric acid from the blood of gouty patients and to relieve their gouty symptoms by causing them, for several hours daily and for several weeks, to inhale air charged with radium emanations. According to *Gudzent,* sodium urate is changed by them into other more soluble substances. This, if true, would explain the absorption of the uratic deposits and the disappearance of uric acid from the blood. (See also *His, Richet, Loewenthal u. Wohlgemuth.*)

Nothing is known about the direct action of electric energy on the metabolic processes of the cells.

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3. WATER AND SALT ACTIONS

Osmotic Tension.—If a certain number of gas molecules are introduced into a vacuum with elastic walls, they seek to increase the volume of the vacuum by distending the walls. The degree of this gas pressure is proportional to the number of molecules in the unit of space, their concentration, and to the absolute temperature. If a given number of molecules or ions are introduced into a quantity of water surrounded by elastic walls, they too tend to increase the volume of the water and to distend the containing walls, which absorb the water on the outside and allow it to enter into the water contained within them. This water absorbing or attracting pressure is, like the gas tension, proportional to the concentration of the molecules or ions in solution and to the absolute temperature. The passage of water through the membrane is called osmosis and the pressure exerted is called osmotic pressure or tension. Gas tension and osmotic tension are analogous.

Isotonicity.—As all the protoplasm of the cells of the animal body is more or less permeable to water and is bathed in watery media, such as lymph, blood-plasma, etc., it follows that the osmotic tension—*i.e.,* the molecular concentration of the substances which exert osmotic tension—must be the same in the cells and in the surrounding media, for otherwise the volume of the cells would be constantly changing. The cells and the surrounding media must be *isosmotic* or *isotonic* to each other. Actually this is approximately the case, all the living cells of the mammal having the same osmotic tension as the fluids present in its tissues. This tension corresponds closely to that of 0.9 per cent. NaCl solution, 0.154 mols, per litre, 1 mol or gramme molecule equalling 58.5 gm. NaCl. This osmotic tension is due only in the slightest degree to colloid substances (proteids, etc.), being almost entirely determined by dissolved crystalloids, chiefly salts (the chlorides, carbonates, and phosphates of the alkalies).

The colloids may be looked upon here as forming a sort of membranous framework which pervades the cells, its outer layers forming an external membranous shell which may be considered as concentrically continued into the interior of the cells. Most animal cells lack a specially differentiated cell membrane.

If the osmotic tension of the body fluid be altered by the introduction of water or of salts, a difference of tension between them and the tissue cells results, and the latter will contract or swell up according as the tension is increased or diminished. However, if the colloids of the cell are equally permeable to the molecules in solution (salts, etc.) and to water, or equally impermeable to both, its volume will remain unchanged, in the first case because no difference in tension arises and in the second because the impermeable walls prevent any equalization of the tension.

Slight differences in tension, such as arise during the changing play of the absorption and excretion of substances, are compensated for by the cells without harm, just as is the case with other normal variations in the conditions of life, but more pronounced and especially rapidly produced alterations of osmotic tension cannot be supported without injury.

A quite gradual, even though very decided, increase of the osmotic tension of the surrounding medium may be supported by vegetable cells; and apparently even by animal cells, for they are able to accommodate themselves to higher than normal osmotic pressure if it is produced gradually enough.

Alterations of the osmotic pressure, which under some circumstances do more or less damage to the cells, may be produced by the introduction of large quantities of pure water or of salts. The effects on the metabolism express themselves by an increased excretion of the decomposition products of proteids, especially urea.

PHARMACOLOGICAL ACTIONS OF WATER

Local Effect.—Pure water is a violent poison for organism whose cells are very readily permeable to it. If cephalopods be immersed in distilled water, convulsive movements occur and death ensues in 5–10 minutes (*Phisalix*).

Injection of water directly into the circulation is followed by the passage of hæmoglobin into the plasma, as some of the red blood-cells, the less resistant ones, are destroyed: 100–150 c.c. per kilo will quickly kill dogs and rabbits, while even 30 c.c. can produce fatal results in a few days (*Bosk u. Vedel*).

On the other hand, cells which are less permeable are much more resistant to pure water. However, the disturbing toxic action of pure water is evidenced even in the mouth by a flat, disagreeable taste and in the nasal and pharyngeal mucous membranes by a distortion of their cells when pure water is applied to them. Presumably the superficial epithelium of the gastric and intestinal mucosa

may be similarly affected, and there may thus result an accelerated casting off and renewal of these cells. It is possible that such effects may play some rôle in the treatment of gastric catarrhs by lavage with plain water, or by the drinking of indifferent waters, such as those of Gastein, Wildbad, and many other springs.

If the water is absolutely pure, it is claimed that the local osmotic action may be so great that serious irritation of the stomach may result. To such effects *Köppe* attributes the harmful effect of swallowing natural ice, which, in contradistinction to artificial ice, contains extremely small amounts of salts, and also that resulting from drinking the waters of the "poison spring" in Gastein. Whether this explanation be correct or not is uncertain.

The healthy gastric epithelium is almost impassable for water and for salts, and therefore within wide limits is unaffected by the osmotic tension of the gastric contents. Considering the fact that food, etc., must often remain for a long time in the stomach, it is easy, from a teleologic point of view, to recognize the advantage of this insusceptibility. We owe our knowledge of the fact, that water and substances dissolved in water are hardly at all absorbed by the gastric mucosa, originally to *Hirsch,* whose results have been confirmed by *v. Mering* and by *Brandl.*

If water contains alcohol or CO_2, it is absorbed from the stomach. It is not known whether these substances to a greater or less extent loosen the lipoidal cement between the epithelium or whether they render the epithelium more permeable in other indirect ways.

In the intestines water is rapidly absorbed, and, as a rule, is almost completely excreted by the kidney in the course of several hours.

Effects After Absorption.—It is self-evident that, so long as it remains in the blood and the tissues or is passing through them, pure water will reduce their osmotic tension, but when water is taken at the same time with food, even when several litres are taken, it causes such slight changes in the osmotic tension that it does not appreciably increase tissue change. If, however, large amounts of water are drunk during a period of fasting, its effects on the osmotic tension of the body fluids may result in an increased decomposition of proteid and of fats and carbohydrates (*Heilner*).

It is not possible to form any opinion as to whether or not such a stimulation of metabolism and regeneration plays any rôle in the effects of the water-drinking cures which have been widely used in the treatment of many chronic diseases, such as syphilis, gout, metallic poisonings, etc. In any case, the augmented blood and lymph flow, which necessarily result from the drinking of large amounts of water, must be of some significance for the "flushing out" of the body and the removal of metabolic end products.

While the flooding of the body by water may be counteracted by

increased diuresis, diaphoresis, etc., the converse of this—the removal of water, or dehydration, by thirst cures—causes an osmotic alteration in the opposite direction, which cannot be relieved by physiological regulation, and consequently its effects in favoring the destruction and regeneration of various cells are more energetic and persistent. In *Straub's* experiments the increased nitrogen excretion persisted for some days after abandoning the limitation of the water intake (for lit. *Magnus-Levy, Dennig*).

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PHARMACOLOGICAL ACTION OF NEUTRAL SALTS

Such effects are produced in the purest form when water is abstracted from the tissue cells by the administration of salts in substance or in hypertonic solution. This has been experimentally proven for sodium chloride, nitrates, acetates, and carbonates (lit. *Rost*), and doubtless holds good for all crystalloids which are absorbed by the blood, in so far as the tissue cells are not readily permeable to them and therefore will be affected by changes in the osmotic pressure produced. The exact manner in which the cells are damaged is not known, but it should be remembered here that chemical cleavage reactions may be caused by dehydration through osmotic action,—for example, fibrin may be dissolved with the formation of globulin and albumoses (*Limbourg, Dastre*).

Accordingly, it is more than probable that when large quantities of sodium chloride, or readily absorbable salts, such as potassium iodide or bromide, are administered, a portion of the curative effects obtained may be attributed to an osmotic stimulation of metabolism and cell regeneration. However, the portion of the curative effects thus produced can hardly be very large, for these substances are usually taken with large amounts of water. Moreover, their osmotic action will be limited further by the fact, still unexplained, that the administration of salts actually causes a limitation or retardation of proteid metabolism, if enough water is taken at the same time with the salts to prevent any dehydration of the cells (*Rost*). Such a retardation or limitation of the catabolism in protoplasm has been proven to result from the administration of different sodium salts. Inasmuch as osmotic action—*i.e.*, a dehydrating action—has been excluded, such effects can be due only to an ion action, and in this

case only to the action of the sodium ions, whose concentration in the organism has been increased while that of the other cations. K′, Mg′, Ca′, etc., present in the body has not been altered.

From the fundamental investigations of *Loeb*, *Overton*, and others, we know that any alteration in the normal cation proportions markedly influences various vital phenomena. If this interpretation be correct, the administration with water of corresponding amounts of the salts contained in Ringer's solution * should cause no sparing of proteids or nitrogen retention. Otherwise the above-mentioned effects would be due only to a dilution of the colloids and alteration of the viscosity, the effects of which on the vital processes are still unknown.

A secondary result of the administration of neutral salts is the *loss of alkalies by the body*. Salts which are absorbed with difficulty (the cathartic salts, salts of polybasic acids), as a result of their cathartic action, cause a loss of the alkaline intestinal juices, while readily absorbable salts (those of the sodium chloride group and salts of the monobasic acids) cause a distinct but much smaller loss of alkalies in the urine, for this secretion becomes more and more strongly alkaline with increasing salt diuresis (*Rüdel*). Whether or not the continued use of large quantities of neutral salts results in any damage to the organism is doubtful, for the body possesses the means of protecting itself against loss of its alkalies (see below).

All the same, in this connection it is noteworthy that the long-continued use of the natural alkaline cathartic waters is better borne than that of the neutral ones, and that the continued use of strongly salted food appears to cause a disposition to disease (scurvy), which may be overcome or lessened by the consumption of fresh vegetable juices, such as lemon juice, etc., which contain salts of the vegetable acids with alkalies, which are combusted in the body with the formation of carbonates and therefore act like the alkalies. It is, however, more likely that this curative effect in scurvy is due to the potassium ions present in the vegetable juices antagonizing the poisonous action of the sodium ions with which the body is flooded as a result of consumption of salted foods (*Emmerich*).

The salts of the Glauber's salt group, which are absorbed with difficulty, influence the metabolism in general only in so far as they cause catharsis and thus interfere with the utilization of the food. However, the bitter waters (magnesia waters), even when taken in small non-cathartic doses, diminish the absorption of the fats (*Vahlen*), probably on account of the formation of insoluble soaps with magnesia.

To a slight extent the cathartic salts are absorbed in the small intestine, and of this amount a portion is excreted again into the large intestine (*Hay*). It is clear that during this passage through the portal circulation these salts may exert a " salt action " on the cells of the liver and the intestines, and this may in part account for their favorable effects in diseases of the intestines and liver.

* Ringer's solution for mammals contains 0.9 per cent. NaCl, 0.03 per cent. $NaHCO_3$, 0.042 per cent. KCl, 0.24 per cent. $CaCl_2$.

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ALKALIES

Among the salts, those reacting alkaline occupy a special position. Such are the basic salts or the salts of the weak acids such as the carbonates. The free alkalies, in respect to their action in the organism, are also to be considered as belonging to this group.

In this connection the basic phosphates and the carbonates, the weak alkalies, such as $Ca(OH)_2$ and $Mg(OH)_2$, the salts of the alkalies with vegetable acids, which are oxidized in the organism to carbonates, and, finally, the borates are of practical importance.

Reaction of the Blood.—Blood and lymph always contain large amounts of indifferent carbon dioxide, of which a portion is present in the form of carbonic acid, corresponding in amount to the quantity of the alkalies in solution. Therefore in a theoretical sense blood and lymph are necessarily neutral.*

Potentially, however, the blood is both acid and alkaline, and may be stated to be amphoteric, inasmuch as, without losing its theoretically neutral reaction, it may absorb acids or alkalies, in the first case the CO_3' ions being liberated from their original combinations, in the second, the CO_2 which is always present being utilized to combine with the bases absorbed. Moreover, not only the carbon dioxide but also the latent H' ions of the blood proteids may be brought into action by the addition of alkalies, while, on the other hand, by the addition of acids both of these may again be rendered inactive or latent. Even in the presence of grave or fatal acid intoxication, the reaction of the blood consequently remains almost normal (*Benedikt, Szili, Robertson*). It is thus evident that the determination of the reaction of the blood by the use of different dyes as indicators can give only values which are physiologically incorrect (*H. Meyer, Henderson*). To litmus the blood-plasma, outside of the body, reacts alkaline, because this acid possesses a stronger affinity for the bases than carbonic acid and the acid proteids of the plasma, and consequently deprives them of their alkalies, with which it forms blue-colored salts.

Increased Alkalinity.—As many chemical processes, particularly oxidation,—*e.g.*, that of glucose,—are either accelerated by, or only possible in the presence of, free OH' ions, it would, *a priori*, appear probable that the administration of alkalies would stimulate oxidation in the animal organism as a result of augmentation of the car-

* Inasmuch as in the presence of a high CO_2 tension traces of free carbonic acid are present in an aqueous solution, the plasma may contain traces of free H' ions, and consequently, theoretically, may be very slightly acid. The same holds true, however, also for the potentially basic proteids of the plasma, so that free HO' ions may also be present, and exact determinations have shown that in the blood-plasma there is an exceedingly small excess of the free HO' ions.

bonate alkalinity of the protoplasm. This presumption, even if it should be correct, is distinctly limited in its significance by the fact that, in the normal organism, it is not possible, even by the administration of alkalies in large quantities, to increase the alkalinity of the blood for any length of time, for any carbonate in excess of the normal is almost immediately excreted by the kidney and the intestines (*Raimond, Freudberg*). Moreover, it is altogether uncertain to what extent and how rapidly the cell protoplasm itself takes any part in temporary alterations of the alkalinity of the blood and lymph, a participation that evidently would be of essential importance.

Action of Alkalies on Metabolism.—It has been claimed that the catabolism of proteids and of fats is influenced by the alkalies, but the experiments on animals and on men undertaken for the purpose of investigating such action have given contradictory results, which are also not free from ambiguity in their significance, inasmuch as the "alkali action" cannot be sharply differentiated from the accompanying "salt action." No specific effects on the decomposition of proteids, including the metabolism of purins, nor on the carbohydrate metabolism, have been definitely proven to result from the administration of alkalies, with the single exception that proteid anabolism is temporarily retarded, but this is compensated for in the later periods of the experiment. On the other hand, *A. Loewy's* experiments indicate that it is probable that the alkalies exert a stimulating effect on the oxidation of fat, and *Rubner* and *Rost* have definitely proven that the borates do exert such an influence.

This is in agreement with the well-known reducing effect of Carlsbad and similar alkaline saline waters. On the other hand, it appears that under some conditions certain other oxidative processes may be inhibited by the alkalies, for following the ingestion of large amounts of sodium carbonate or citrate (20–30 gm. per diem) more "neutral" and less "oxidized" sulphur is excreted in the urine (*Jawein*).

Alkalies in Gout.—The manner in which the alkalies produce their reputed favorable action in gout is still unknown. So long as it was believed that gout was due to a retention of uric acid resulting from unfavorable conditions for its solution and the consequent difficulty with which it could be excreted through the kidney, it was natural to explain the value of the alkalies by their supposed power of bringing uric acid into solution. This explanation is, however, certainly incorrect, for such action cannot occur under the conditions which obtain in the organism (*Gudzent*). Further, the recent exhaustive investigations of *Brugsch* and *Schittenhelm* have rendered it extremely probable that in gout it is not the insolubility or the faulty excretion of uric acid, but a retardation of its formation or destruction on account of a defective ferment activity, which is the decisive

pathogenic factor. In addition, exact investigations of the effect of the administration of alkalies on the excretion of uric acid in gout have given results which are by no means lacking in ambiguity (*v. Noorden*), but in the majority of instances the excretion of uric acid was not affected. For these various reasons, *it is exceedingly doubtful whether the alkalies in any way affect the metabolism, solubility, or excretion of uric acid.* The inclination of clinicians is rather to explain the unquestionably beneficial action of alkalies in gout by their curative action on disturbances of the alimentary canal and the liver, which quite often are present in this disease (*v. Noorden*).

Urolytic Action of Alkalies.—On the other hand, the value of the alkalies in the treatment of uratic deposits in the urinary tract is well established and is doubtless due to the increased alkalinity of the urine thus caused. This increase need not be so great as to cause the urine to render red litmus paper blue, but it may always be recognized by the relative increase of the disodium phosphate as compared with that of the acid monosodium phosphate. The beneficial effect of this increase in the alkalinity of the urine is evidenced by the fact that often after a short time small pieces of the concretions are passed out with the urine, and that very often the excretion of uric acid is increased (*v. Noorden*). Among the alkalies, the alkaline earths appear to be especially useful for this indication, and, among these, calcium appears to be the best, on account of the fact that it is free from any disturbing side actions, with the exception of the very occasional formation of large fecal concretions.

These alkaline earths, especially chalk and magnesia, combine with fatty acids and with sulphuric and phosphoric acids in the intestine, and consequently the urine becomes alkaline and at the same time contains less sulphates and less phosphates,—*i.e.*, less salts,—so that its molecular concentration falls. This, too, is of material importance for the more ready solution of the urates, and sufficiently explains the value of these alkalies and of the waters containing them (*Wildungen, Fachingen,* etc.) in the treatment of uratic deposits in the urinary tract (*Caulet, J. Strauss*).

Effects on the Alkalinity of the Blood.—Although, as previously stated, the normal alkalinity of the blood cannot be appreciably augmented by the administration of the alkalies, it is quite otherwise in the presence of abnormally diminished alkalinity of the blood, such as occurs in exogenous and endogenous acid intoxication.

Carnivorous animals, and to some extent also vegetarian animals and man, are able to protect the alkaline carbonates and albuminates of their blood from decomposition by acids, by utilizing the ammonia, formed during the breaking down of proteids, for the neutralization of any abnormal amounts of acid, instead of transforming it as usual into carbamic acid and urea. This is the explanation for the fact

that the quantity of ammonia excreted in the urine is invariably increased in acid intoxication of any type (*Loewi*). However, this protective regulation of the organism is a limited one, and, if enough acid be administered or produced, it may be so inadequate that the carbonate alkalescence of the blood will be decidedly diminished.

This occurs in diabetic coma as a result of the formation of oxybutyric acid, or when abnormal amounts of lactic acid are formed as a result of excessive muscular exertion, and in many poisonings, such as those produced by arsenic, phosphorus, etc., and in the toxæmia of fever. *F. Kraus* found the alkalinity of the blood, in terms of the CO_2 removable by the vacuum pump, diminished to ½ or ⅓ of the normal in typhoid fever, erysipelas, and scarlatina, and in tuberculosis with continuous fever. As this diminution of the alkalinity persists in such cases even when the temperature is artificially lowered, it is evident that it does not depend on the increased temperature but is due to the toxic decomposition of proteids. The deficit in alkaline carbonates in the blood and its more or less harmful effects may be lessened or removed by the administration of the alkaline salts of the vegetable acids, the citrates being especially adapted for this purpose, as they are almost completely combusted in the body with the formation of carbonates.

Especially in severe diabetes mellitus large amounts of oxybutyric acid are formed which greatly diminish the alkalinity of the blood by expelling the combined carbonic acid. In extreme cases, instead of 30–36 per cent. by volume, *Kraus* found only 12.4 and 9.8 per cent of carbonic acid in the venous blood, while *Minkowski* found as little as 3.3 per cent. It is clear that in such cases the administration of alkalies will be beneficial and even life saving (*Magnus–Levy*). It is claimed that calcium carbonate and phosphate exert an especially favorable influence in diabetes. In addition to their action as alkalies, their value is probably in part due to the fact that the diabetic appears to lose his calcium more readily than the other alkalies and therefore has a greater need for this particular element (*Schlesinger u. Gerhardt.*)

Other Actions of the Alkalies.—In addition to the effects on metabolism discussed above, the alkalies by their local actions produce a number of therapeutically important effects. Concentrated potassium hydrate solutions decompose and destroy organic substances, even such resistant ones as the horny structures of the skin, in which process their power of saponifying and dissolving the protective fat in the skin is of more or less assistance. They are, therefore, used externally in different concentrations as caustics and as means of irritating, softening, or cleaning the skin. Vienna caustic paste, potassium soaps, sodium hydrate, and potash may be used as counter-irritants or as disinfectants in scabies. Sodium soaps are used for cleansing purposes or as mild irritants in enemata. Borax may be

employed as a lotion or in mouth washes. Internally dilute solutions of the alkaline carbonates or of $Ca(OH)_2$, compound chalk powder, magnesium oxide, may be used for the direct neutralization of acids in the stomach or intestines or to stimulate [? Tr.] the gastric digestion (*Pawlow*) or to dissolve mucus (see Pharmacology of the Digestion, p. 165).

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ACIDS AND ACID SALTS

The administration of acids may affect the gastric and intestinal digestion and in this way influence the metabolism (for details see Pharmacology of the Digestion, p. 165). During and after their absorption they neutralize the alkalies of the blood and of the tissues, and thus diminish their normal content of alkaline carbonates and albuminates in so far as ammonia by its vicarious action does not prevent this. *A priori* it is probable that the metabolic processes will be affected by such diminution of the alkalinity of the tissues, and that this is so is indicated by the manner in which autolysis is influenced by diminished alkalinity. Post-mortem autolysis of the organs, which appears to resemble closely the catabolic processes of life, is markedly influenced by the reaction of the surrounding medium, alkalinity, corresponding about to that of normal serum, strongly inhibiting it and, on the other hand, a slight acidity markedly accelerating it (*Hedin u. Rowland, Wiener, Loeb u. Bär*).

In accordance with this, an increased destruction of proteids would be expected to result from the administration of acids, and, as a matter of fact, this effect has been observed in men who had taken inorganic acids in small amounts, for they excreted not only more alkalies and ammonia but also more sulphuric and phosphoric acids

than normally (*A. Keller, Dunlop*). In severe acid intoxication (in rabbits) the production of heat is diminished and there is a lessened formation of carbonic acid and a diminished consumption of oxygen (*Chvostek*).

From these results and from what has been said previously it might be concluded that the proteid metabolism—*i.e.*, its decomposition and cleavage—is retarded by the alkaline carbonates of the blood, while oxidative processes, such as the combustion of the fats and carbohydrates, are accelerated, and that, on the other hand, a diminution of the alkalinity of the blood by either exogenous or endogenous acids has the opposite effect. Such endogenous acidification, due chiefly to the formation of lactic acid, always occurs when the tissues are very inadequately supplied with oxygen, either on account of an insufficient transportation of the oxygen by the blood or on account of chemical inhibition of the oxidases of the tissues. Such disturbances will necessarily also influence metabolism in a corresponding fashion, and in extreme cases will cause on the one hand increased destruction of the tissues and on the other fatty degeneration (*A. Fränkel, M. Fisher*).

Besides producing an alteration of the metabolism, the neutralization of the alkaline carbonates of the blood which occurs in extreme acid intoxication has an extremely harmful effect on all nervous organs, the vasomotor centres, the respiratory centre, and the motor ganglia of the heart being depressed or paralyzed. Under such conditions the intravenous injection of sodium carbonate may, even at the last moment, have a life-saving effect.

Locally, concentrated acids produce a caustic and destructive effect on the tissues, while dilute acids cause slight irritation or stimulation or produce an astringent action and may be used therapeutically for such effects. Those acids which, on account of their lipoid solubility, readily penetrate the skin, such as acetic and formic acids, are especially useful as skin irritants. Sulphuric acid and others may be used in the form of baths for similar purposes.

Carbon Dioxide as a Stimulant to the Nervous System.—Among the acids, carbonic acid occupies a peculiar position. In so far as it reacts with free alkalies or with those combined with the weaker acids (albuminates) it acts as an acid. In addition it acts as neutral CO_2 which is always present in the tissues and in the blood, in which form it produces stimulating and depressing effects just as do other neutral substances which are soluble in water and lipoids,—*i.e.*, the substances belonging to the group of ether and alcohol. The normal CO_2 tension of the tissues, which amounts to about 6 per cent. of an atmosphere, is of decisive significance for the maintenance of the normal excitability of the tissue cells and, as a matter of fact, is an absolutely necessary condition for its maintenance. If as a result of too extreme ventilation of the lungs the

carbon dioxide tension falls markedly, acapnia results and the nervous system loses its excitability, and collapse and shock develop (*Y. Henderson*).

A. Mosso at one time attributed the phenomena of mountain sickness to such a deficiency of carbon dioxide, but did so incorrectly, as has been shown by both older and newer investigations (*Zuntz, Loewi, Miller u. Caspari, Boycott* and *Haldane*).

If, on the other hand, as a result of relatively or absolutely insufficient elimination by the lungs, the carbon dioxide content of the blood is increased beyond the normal, restlessness and excitation of the respiratory and vasomotor centres develop, while, if the increase be great enough, deep narcosis is caused.

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THYROID SUBSTANCES

Iodothyrin, or thyroiodin, an iodine-containing substance, was first prepared from the thyroid glands by *Baumann* in 1896. It is obtained from a proteid containing iodine, **thyroglobulin**, by the action of heat and hydrochloric acid. In all probability this iodine-globulin is a secretion of the thyroid glands which enters the blood and exerts an important influence on the normal growth and death of the cells of all the organs of the body. It is for our present purpose of little importance whether this internal secretion or hormone produces this " life-stimulating " action directly by a catalytic acceleration of chemical reactions * or indirectly by destroying an inhibiting substance. Thus far there is no evidence which forces the acceptance of this latter assumption, the " detoxication " hypothesis.†

* Recently *L. B. Stookey* and *Vera Gardner* have reported that the autolysis of organs obtained from dogs thyroidectomized 5 to 10 days earlier proceeds more slowly than that of the organs obtained from normal animals. They also state that the oxidizing power of such organs, estimated by the oxidation of indol added to an emulsion of the organs, is weaker than that of emulsions of the normal liver, spleen, and kidney. Moreover, both the autolysis and the oxidizing power can be distinctly increased if normal dogs be treated for a long time previously with KI, probably as a result of an increased function of the thyroid glands (see the section dealing with iodine, p. 398).

† For the influence of the thyroid glands or iodothyrin on the functions of the heart and vessels see *v. Cyon*, Die Gefässdrüsen, Berlin, 1910, and *Biedl*, Die innere Sekretion, Wien, 1910.

In Hypothyroidism.—If the thyroids be absent, as in thyreopriva, cachexia strumipriva, or myxœdema, or if they be degenerated, as in endemic cretinism, the formation of the blood and the general growth are retarded and more or less complete myxœdema develops. Under such conditions the transformation of energy and the tissue change may be diminished to as little as ½ of the normal (*Magnus-Levy*). If, however, iodothyrin be administered to such individuals, the transformation of energy and the metabolism both rise to, and in fact at times above, normal levels, and those cases in which development had ceased or in which atrophy has occurred regain the capacity of active growth and regeneration. As a result of such observations, of similar significance whether made on animals or on human beings, there can be no doubt that iodothyrin possesses the property of truly stimulating metabolism,—*i.e.*, of stimulating both the anabolism and catabolism of the cell protoplasm,—and this stimulation apparently affects all types of cells, including the cells of the nervous system. The successful treatment of infantile cretinism and of myxœdema by thyroid preparations is one of the most brilliant therapeutic achievements which have been rendered possible as the result of experimentation.

Parathyroids.—Cachexia strumipriva, following the extirpation of goitrous thyroids, is complicated by tetany only in case the parathyroids have also been removed or if they have been so injured during the operation that they degenerate in their entirety. In this serious condition the administration of thyroid glands is of no avail, nor does any benefit result from administering parathyroid tissue internally, subcutaneously, or intravenously (*Pineles*). The parathyroids appear to be capable of performing their functions only when undisturbed in their own proper situation. Their function is probably that of rendering harmless certain unknown metabolic products.

In normal animals and human beings, the administration of iodothyrin causes a similar stimulation of the metabolism, although naturally not to the same extent as in those cases where the function of the thyroid was previously entirely lacking or very insufficient. In many cases the normal optimal total transformation of energy cannot be augmented, but in others by continuous administration of iodothyrin for 2 to 3 weeks it can be increased about 2.5 per cent. Regularly and from the start the excretion of nitrogen is increased by the administration of iodothyrin, as a result of a more active decomposition of proteid material. Consequently the nitrogen balance becomes negative and a loss of weight results (for lit. see *Magnus-Levy*).

In Obesity.—The augmentation of oxidation by thyroiodin has been observed especially often and in high degree in obese individuals, in whom it is not seldom accompanied by marked loss of fat. This, however, by no means holds good for all obese patients, and especially not for those in whom there is no pathological disturbance of metabolism but who have become fat essentially as a result of overeating.

It appears that this increase of fat combustion occurs especially in constitutionally obese individuals who, in spite of scanty diet and exercise, are unable to burn up their fat. One is tempted to assume that in these cases the abnormal metabolism is due to a partial insufficiency of the thyroid function or that of other glands whose functions are of a similar nature. If this be so, the success of the treatment with thyroid glands explains itself.

The exaggerated production and accumulation of fat, when the thyroid is insufficient or absent, appears to be due not only to the general retardation of oxidative processes but more particularly to the facilitation of the transformation—*i.e.*, the reduction—of the carbohydrates to fats, which results from this inadequacy of these glands. Certain clinical observations render it probable that the functionally active thyroid moderates or inhibits this normal transformation of the carbohydrates to fats, for not infrequently, especially in obese patients who are predisposed to diabetes, the administration of thyroid preparations causes glycosuria (*v. Noorden*).

Symptoms of Iodothyrin Poisoning.—A number of different disturbances—rush of blood to the head, palpitation and acceleration of the heart, dyspnœa, sleeplessness, tremor, thirst, subjective feelings of heat, excessive sweating, swelling of the neck, and exophthalmos—have been observed to follow immoderate or careless administration of iodothyrin to susceptible individuals. These are all symptoms which are characteristic of the picture of Graves's or Basedow's disease. This similarity in the symptoms of the poisoning with iodothyrin to the symptoms of this disease is not only a superficial one but is one based on the similar nature of the two conditions. Almost conclusive proof of this essential similarity has been furnished, on the one hand, by the cures which are obtained in Graves's disease by the surgical removal of a portion of the hyperactive thyroid gland, and, on the other, in the almost certain demonstration of an increased amount of iodothyrin in the blood of patients with this disease (*Reid Hunt*).

This author has discovered in the varying resistance of mice toward the highly toxic acetonitrile, CH_3CN, an exceedingly delicate test for iodothyrin. Feeding of minimal doses (1/10 mg.) of dried thyroids increases this resistance 200 per cent. or more. Other organic substances, including normal blood, possess this power not at all or only to a minimal extent, but the blood of patients with Graves's disease does possess it.

These undesirable and at times dangerous effects of the therapeutic administration of thyroid, particularly its power of increasing the decomposition of proteids, constitute a limitation for its employment which should not be disregarded. For therapeutic employment, as a rule, dried thyroid substances from calves or the powdered dried extract, or thyroiodin mixed with sugar (1.0 gm. = 1.0 gm. dried thyroid), are employed.

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OTHER INTERNAL SECRETIONS

The thyroid is not the only gland exerting an influence on metabolism. The **hypophysis** and the **genital glands** through their internal secretions certainly exert an influence on metabolism and growth, and especially on the development of the bony skeleton. Hypoplasia of the genitals causes retarded and incomplete calcification of the epiphyses and infantilism, while hypertrophy of the hypophysis causes stimulation of the growth of bones, acromegalia. Both of these glands appear to stand in an intimate relationship with each other and with the thyroid, although up to the present not much is exactly known about this (see in this connection *A. Frölich, Biedl*).

The ancient observation that castration causes an increased accumulation of fat has been investigated in animals by *Loewy* and *Richter,* who found that it caused a retardation of metabolism and of oxidation, which, however, according to *Lüthje,* does not occur in all cases. That these effects, when they do occur, are due to the absence of the internal secretion has been proven by the fact that the administration of ovaries or testicles can again stimulate the diminished metabolism, while in normal animals their administration produces no such effect.

That the **suprarenals** also exert an influence on the general metabolism is probable, for the anomalies of metabolism which are present in Addison's disease are best explained on this assumption. These observations have, however, not led to any therapeutically well-grounded or practically useful results for treatment.

Still less well grounded is the employment of numerous **other organotherapeutic** preparations, such as those obtained from the brain, kidney, and other organs, which under various names are advertised with unreserved laudation.

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IODINE AND IODINE COMPOUNDS

While iodine must also be numbered among those substances especially affecting the metabolism, it does so in a peculiar and limited degree and only indirectly.

Local Action.—When brought in contact with living tissues in concentrated solution, as in the tincture of iodine or in Lugol's solu-

tion, it produces in them substitution products and oxidizes them, just as it does all labile organic substances. Consequently it produces a destructive action in the superficial tissues and causes a more or less marked inflammatory reaction. That portion of the iodine which is not fixed at the point of application is absorbed in combination with proteids or lipoids or in the form of salts and can then exert its peculiar systemic actions.

Systemic Actions.—These general actions are exerted essentially by all readily decomposed substances containing iodine, by iodine itself, and by the iodides, as also by iodoform or iodized fats, etc. Consequently the therapeutic indications for the internal administration of all these preparations are similar, for *with all of them their effects are due essentially to an "iodine action."* This is especially true for the iodides.

The **iodide of potash** is a very soluble and readily absorbed neutral salt and as such naturally exerts the same osmotic "salt action" as does sodium chloride. The peculiar actions, however, which give to it a special therapeutic value not possessed by the other halogen salts are, without doubt, to be attributed to the iodine which is set free from it by oxidation.*

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* In this connection reference is often made to the ion actions of iodine, but this cannot be taken for granted without further evidence. A solution of KI contains iodine ions with a negative charge, just as a solution of KCl contains chlorine ions with a similar charge. However, as far as we know, these latter exert no special actions. Of them we know only that they are necessary for the life of the organism, and are retained by it with great tenacity, even when the diet contains no chlorine.

Up to the present no one has conducted any investigations with the object of finding out what special physiological actions are exerted by the iodine anions. However, they cannot be very important, for anion actions must, like all ion actions, start abruptly and by their direct actions cause noticeable disturbances. However, large amounts of NaI may be taken by mouth or injected subcutaneously or intravenously without causing any noticeable direct disturbances, the toxic action developing, if at all, only after several days, and being, therefore, probably the result of secondary chemical changes (*Berg, Sgalitzer, Stockman,* and *Charteris*). *Barbera's* contradictory results obtained by injecting a 20 per cent. NaI solution into the veins do not permit of any positive deductions.

That action which we know as "iodine action" is, however, not to be attributed to the iodine anions but to the iodine molecules, for it is these which form organic combinations with various organic constituents of the body. *It must consequently be assumed that the HI is set free from KI in the organism and by oxidation is transformed into I_2 and that then this produces the specific actions, perhaps after ionization in the form of I cations.*

If HCl were as readily oxidizable, NaCl would exert Cl actions. HCl is, however, hardly at all affected by oxidizing agents, while HBr is readily and HI even more readily affected by them, and consequently specific iodine and bromine actions may result from their administration. In accordance with the law of mass action, a small portion of the halogen salts is always hydrolytically dissociated in the body by the CO_2 tension which is always present. Free HI and HBr are very unstable and undergo oxidation even under the influence of atmospheric oxygen. *Binz* has shown that KI is oxidized by living protoplasm in the presence of CO_2.

The **iodides** and the **iodized fats**, in their behavior, stand in about the same relation to iodine as does atoxyl to arsenious acid (see p. 535). They can, like atoxyl, circulate about in the body as substances which, for the time being, are indifferent or inactive and, wherever the necessary conditions are present, give off free iodine and allow it to act, while by all means the largest part of the administered preparation is excreted in unaltered form or, in the case of iodized fats, deposited in various indifferent locations. Substances which, like iodoform, act as undecomposed molecules will naturally exert actions made up of these specific actions and of iodine actions.

Iodine possesses no power of influencing the metabolism, in the usual sense in which this phrase is used, for neither experiments on man nor on animals have demonstrated that it exerts any constant influence on the transformation of energy or on tissue change. Such action is indicated only by a series of clinical observations, such as the striking emaciation which occurs in some, but by no means all, individuals who, for a long time, have taken iodine or KI internally, and the atrophy of certain glandular organs, especially hyperplastic thyroids and the mammary glands, which may also occur under similar conditions. This general emaciation is, however, certainly not a direct effect of the "iodine action."

Effects on Mucous Membranes.—The continuous use of iodine preparations very often causes an active congestion with painful swelling and hypersecretion in the mucous membranes of the nose, throat, and conjunctiva and also of the pharynx and larynx, while more rarely the mucous membranes of the alimentary canal may be affected, especially if a complicating nephritis interferes with its excretion in the urine (*v. Noorden*).

Effects on the Skin.—In a similar fashion inflammatory irritation of the skin occurs, with acne postules, furuncles, or purpura, all probably the effect of the free iodine which is formed by oxidation from the iodine excreted in the glands of the skin.

Effects on Nutrition.—These inflammations of the mucous membranes, especially if they affect the stomach, can produce a marked disturbance of nutrition and may occasionally lead to emaciation. Ordinarily, however, even after the use of large amounts of KI for months at a time, this does not occur except in certain patients with goitre.

Effects on the Thyroid.—In such individuals the administration of iodine in any form is followed, often after a few small doses, by the development of the typical clinical picture of thyroidism or Graves's disease, with the rapid loss of weight and strength characteristic thereof (*Brewer, Pineles*). *It may consequently be concluded that iodine influences the metabolism only indirectly, through the thyroid glands,* and to an appreciable degree only in case the thyroid tissue is hypertrophic but at the same time functionally insufficient. Such

conditions of the thyroid are present in many cases, and are due in all probability to a too small amount of iodine in the glandular tissue.

It is well known that the physiological activity of the thyroid gland is determined by the amount of thyroiodin present in it and that the poorer it is in iodine the less active it is. This has been proven experimentally by *Oswald, Roos,* and others, and in a very peculiar fashion by *Reid Hunt* and *Atherton Seidell. Halsted* states that the lack of a sufficient amount of active iodothyrin in a thyroid causes the hypertrophic formation of glandular tissues which are poor in colloids and, therefore, chemically and functionally insufficient. The new-born offspring of animals deprived of their thyroids have markedly hypertrophied but colloid-free thyroids (*Halsted, Edmunds, A. Kocher, Reid Hunt*), and hyperplastic human or animal thyroids contain little or no iodine (*Oswald*). On the other hand, the amounts of thyroiodin contained in the thyroid is increased by the administration of KI or other iodine preparations, while the hyperplastic tissues poor in colloids atrophy and the goitre diminishes in size.

From all this it can hardly be doubted that iodine changes the functionally weak thyroid tissue which is poor in iodine into one rich in iodine and physiologically active, and that in this way it causes the disappearance of the superfluous hyperplastic glandular tissues. This conception of the action of iodine enables us to understand the pronounced augmentation of the catabolic processes in the whole body which sometimes, particularly in cases of thyroidism, occurs under the influence of iodine medication and which may be accompanied by temporary febrile manifestations. From the foregoing it is clear that the iodine treatment of goitre, introduced by *Coindet* in 1820, rests upon a physiological basis.

In Scrofula.—Whether or not the benefits resulting from the iodine treatment of scrofulous swelling of the lymph-nodes are to be explained in the same fashion is uncertain, particularly as no attempt has been made to determine whether or not the scrofulous diathesis of many (but by no means all) tubercular patients is dependent on an insufficiency of the thyroid. It is possible that in these cases the favorable results are due to a direct action of iodine which accelerates the decomposition or destruction of the pathological tissues. It is also possibly of significance that tubercular tissue absorbs iodine more strongly than normal tissues (*Loeb u. Michaud*).

In Syphilis.—The same question arises in connection with the symptomatic curative effects of the iodides in syphilis. There is no doubt that under their influence there occurs a rapid degeneration and disappearance of syphilitic lesions, especially those of the second and third stages, but a definite cure, with prevention of relapses, is not obtained by the use of the iodides. A definite etiotropic * action cannot be attributed to it.

* An etiotropic action is an action directly on the specific organism causing a disease.

In Atheroma.—The alleged curative action of iodine in atheroma is quite as difficult of explanation. The functional disturbances occurring in arteriosclerosis which are due to the faulty blood flow through various organs—*e.g.*, in cerebral arteriosclerosis and angina pectoris—are often distinctly benefited by KI if the condition is not too far advanced. According to *Romberg*, this is due to this drug's power of diminishing the alkalinity of the blood, which change permits of a more ready flow of blood through the atheromatous vessels (*O. Müller u. Inada*). How this effect is brought about is not known (*Adam*). The alleged vasodilating action of KI does not exist (*Stockman* and *Charteris*). *Thaussig's* observations of a diminution of the hypertension of the vessels in chronic lead poisoning, which he explained as due to a vasodilating action, are the result of the accelerated elimination of the lead, which results from the administration of iodides.

The beneficial action of iodine in *nervous asthma* * and in *neuralgias* is altogether incomprehensible, but its beneficial effect in *chronic lead* and *mercury poisoning* has been understood since it was shown by *Melsens* in 1844, and later by others, that the elimination of these two metals is distinctly accelerated by the administration of the iodides.

Administration.—For the various indications mentioned, the iodides of potassium and of sodium are administered in doses ranging from 0.1 gm. up to 20.0 gm. or more per day, or the newer organic iodine combinations, such as *iodipin* and *sajodin*, may be employed. The former is a combination of iodine with the unsaturated fatty acid of sesame oil, and is obtainable in two strengths, one containing 10 per cent. and the other 25 per cent. of iodine. Sajodin is a calcium salt of a fatty acid and contains 20 per cent. of iodine.

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* See page 347.

QUININE

As other physiological and therapeutic actions of quinine will be discussed elsewhere (pp. 470 and 527), our attention will here be directed only to the direct effects of this drug on the chemical activities of living cells.

The antipyretic action of calisaya bark, which has been known ever since its introduction in medicine, and the improvement in the general state of nutrition of run-down individuals which results from its administration, early indicated the propriety of investigating its effects on metabolic phenomena. Even to-day quinine enjoys a reputation as a tonic or means of improving the general health.

The main facts concerning the actions of quinine on metabolism may be stated briefly as follows. Quinine retards all the vital processes of the cells, inhibiting both anabolic and catabolic reactions. In this fashion, even small doses of quinine possess the power of sparing the tissues of the body, but when its effects are produced in the highest degree it acts as a general destroyer of life, and causes a complete cessation of the production of energy. On what elementary action this depends is entirely unknown. We know only that it may be observed in almost all living organisms, in the lower and higher plants, in protozoa, and higher up in the scale of life. Probably it is due to an action on the enzymes, which are, as it were, the chemical tools of the cells, for pure enzyme actions are weakened or entirely inhibited by quinine (*Laqueur*), which possesses the power of inhibiting oxidative and synthetic reactions, such as the formation of acid in the blood, the guaiac reaction, the formation of hippuric acid in the kidney, the phosphorescence of phosphorescent bacteria, and also the hydrolytic and catabolic reactions in living or surviving organs.

Consequently, in neither the lower nor the higher organisms does quinine cause a stimulation of vital processes or of regeneration or stimulation of growth, such as is observed under the influence of thyroiodin.

Even the apparent stimulation of muscular power, which is observed at the start of the quinine action, is not the result of any true increase in the production of energy, although, according to *Santesson*, there is at first an augmentation of muscular work, which, however, is quickly followed by a correspondingly more rapid exhaustion. This may be attributed to an inhibition of anabolic processes, as is done in connection with the analogous action of alcohol (*Fröhlich*, *Lee*). Particularly for quinine this appears to be the correct explanation.

All exact observations agree in indicating that the proteid metabolism is diminished by quinine, the nitrogen balance showing that less nitrogenous material is decomposed when quinine is given than is normally the case. This is true in health and in fever, when food is taken or when the patient is fasting (*Loewi*).

As under normal conditions the central heat-regulating mechanism, which is hardly at all narcotized by quinine (on the contrary,

it is perhaps slightly stimulated at the start), sees to it that the lessening of heat production is compensated for by diminished heat loss (*Gottlieb*) or by an increased oxidation of non-nitrogenous substances, under normal conditions, doses, which are not too large, do not alter the total transformation of energy as measured by consumption of oxygen and excretion of carbon dioxide, nor, as a rule, do they produce any alteration in the body temperature, except that occasionally in nervous or excitable individuals such doses may at first cause a slight rise in temperature (*Fr. Müller*).

In Fever.—If, however, the heart-regulating mechanism is inadequate and readily fatigued, as is the case in infectious fever, the general inhibitory effect of quinine on the chemical processes in the body causes an alteration of the respiratory exchange of gases, due to a diminished oxidation of all substances, both nitrogenous and non-nitrogenous, and the total production of heat is diminished (see Antipyretics, p. 470). The direct effect of quinine on the central nervous system, which may cause motor restlessness and increase of the respiratory volume, and its effects on the circulation, namely, acceleration of the heart-rate, may mask this fundamental action on metabolism.

From the foregoing it may be seen that a therapeutic invigorating effect on the metabolism, leading to an improvement in the nutrition, is not to be expected from quinine, for it certainly does not favor the formation of new cell material and probably inhibits it. However, it may exert a conservative sparing action, particularly in such conditions as thyroidism, infectious fever, etc., in which the catabolic processes are abnormally increased as a result of pathological stimuli and in which there is a rapid loss in weight and strength. *Quinine may be said to retard the processes not only of life but also of dying.*

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SUBSTANCES INHIBITING OXIDATION (*"Arsenic Group"*).

Lack of Oxygen.—Augmentation of the normal—apparently optimal—oxidation of the blood produces no effects on the metabolism, but diminution thereof produces very important effects, which, in their character and intensity, vary greatly with the more or less insufficient supply of oxygen.

A slight diminution of the oxygen tension in the atmospheric air, such as is met with in altitudes of about 1000 metres above the sea level, causes an increased production of new red cells and probably also of other tissues, particularly of the muscles, for with the same

intake of food much more nitrogen is retained than corresponds to the newly formed hæmoglobin (*Jaquet, Jaquet u. Stähelin*). *v. Wendt's* careful experiments on himself at heights of between 3000 and 4500 M. showed that, in addition to a marked retention of nitrogen, there is a retention of sulphur and iron and also increased assimilation of phosphorus. The respiratory exchange of gases is also increased under these conditions, a fact probably of much importance in connection with the therapeutic effects of the high altitudes.

Very insufficient oxygen supply, on the other hand, such as results from severe hemorrhages, anæmias, and dyspnœa, leads to a marked and readily recognizable disintegration and degeneration of tissues, with fatty degeneration and abnormal production of acids, and to a retardation of synthetic processes, such as that of hippuric acid in the kidney, etc., and finally to paralysis of all functions.

Just as a moderate insufficiency in the oxygen supply causes a favorable stimulation of the metabolism and the retention of nutritive material, and as a more pronounced deficiency causes an increased destruction of tissues, a number of chemical agents produce the same results. It, therefore, is not improbable that their action in the last instance depends on their power of preventing the protoplasm from utilizing oxygen (*Loewi*). The more important of these substances are:

(a) Phosphorus.
(b) Arsenic and antimony and their compounds.
(c) Iron and mercury.

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PHOSPHORUS

It is only the chemically active yellow phosphorus which possesses a pharmacological action, and it appears that only phosphorus itself and not its combinations produce these effects, for there are no known compounds containing it which produce the same or even similar actions (*Schuchardt*) unless nascent phosphorus is set free from them (*Santesson*).

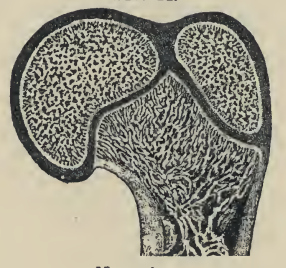
Phosphorus is very slightly soluble in water, but fairly so in many organic solvents and in fats. It is slowly absorbed from the alimentary canal, and its characteristic effects develop only slowly and gradually. In the body it appears to be hardly oxidized at all extra-cellularly, for it remains unaltered when suspended for days

in arterial blood (*H. Meyer*), although outside of the body it is very readily oxidized when exposed to air.

Effects on General Metabolism.—When taken in very small *amounts* (½–1 mg. per diem in man) *phosphorus stimulates metabolism, causing an increased growth and new formation of tissues.* While exact metabolism experiments on children or young animals have never been made, this may be concluded from the favorable effects on the general state of nutrition observed by clinicians and from the unusual increase in the weight of rhachitic children to whom phosphorus has been given (*Kassowitz, Hagenbach, Neumann*). On the other hand, we possess a more exact knowledge of its effects on the blood and on the bony tissues.

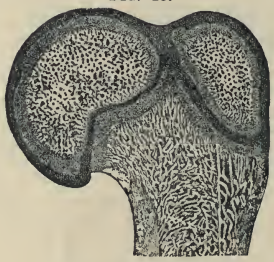
On Blood.—Among the first effects of the action of phosphorus in man is an increase in the number of red blood-cells (*Gowers, Thaussig*), and even after large toxic doses the production of the

Fig. 44.



Normal.

Fig. 45.



After phosphorus.

Figs. 44, 45.—Heads of calves' femur (from Wegner).

red cells appears to be increased beyond the normal, for in severely poisoned mammals their number is not, as a rule, diminished, although the markedly increased production of bile pigments indicates an increased destruction of the red cells * (*Stradelmann*).

On Bone.—Phosphorus influences the formation of bone very markedly. In young animals the growing portion of the epiphyses forms a compact bone instead of a spongy substance and the osseous tissue hypertrophies at the expense of the medulla (*Wegner*) (Figs. 44 and 45). These effects appear to be similar to those which *Schiff*, after dividing the nerves of the leg, observed in the bones of the leg and foot of young animals as the result of the continuous congestion and inflammatory irritation from a wound. Phosphorus thus undoubtedly stimulates the growth of bone, or, otherwise expressed, causes the anabolic processes in the metabolism of bony tissues to

* In the chicken, while the destruction of these cells is at first so great as to more than keep pace with their new formation and their number is markedly diminished, the rapid return to normal numbers shows that the new formation of the red cells takes place very rapidly (*Gowers, Thaussig, J. Vogel*).

preponderate over the catabolic ones. By chemical analysis *Kochmann* has demonstrated a relative increase in the calcium of the bones under the influence of chronic phosphorus poisoning. This increase amounts to a change of from 21 per cent. to 25 per cent. of the dried residue.

Toxicology.—The harmful effects of poisonous doses of phosphorus manifests itself to a much greater degree in the metabolism of the other organs. Morphologically it may be readily recognized macroscopically in the liver, heart, and kidneys, and to some extent in the diaphragm and the other muscles, all of which show fatty degeneration to a greater or less extent. In the liver and in the heart, this fatty degeneration is due to the fact that fat from other tissues is deposited in them (*Loewi*), but in the kidneys it appears to be due to the fact that the fat and lecithin normally present in them, but, as it were, hidden or combined, is set free and becomes visible (*Rubow, Mansfeld*). As the capillary epithelial cells also are the seat of fatty degeneration, small hemorrhages readily occur. By chemical analytical methods it may be shown that phosphorus causes a greatly increased destruction of the tissues, with marked disturbance of the synthetic, oxidative, and cleavage reactions.

The consumption of oxygen and the formation of CO_2 is lessened. Less fat and correspondingly more carbohydrates and proteids are combusted, which latter, however, are only in part completely broken down, so that considerable quantities of intermediary metabolic products (amino acids, peptones, lactic acid, and many others) are present in the blood. In agreement with this, there is a marked augmentation of the autolytic decomposition of proteid in the livers of animals poisoned by phosphorus, as compared with normal organs (*Jacoby*). Moreover, the addition of phosphorus to the perfused blood strongly inhibits the synthesis of hippuric acid in the isolated kidney (*Hauser*).

As has already been mentioned, these disturbances of metabolism agree in many particulars with those resulting from the lack of oxygen, and it is consequently not at all improbable that *phosphorus renders the body cells less capable of utilizing oxygen in the normal fashion.*

In its effects on function, phosphorus poisoning manifests itself by a progressive diminution in the functional power of all the organs. The cells of the brain become incapable of performing their normal functions, and the poisoned individual falls into a state of apathy and unconsciousness,—sometimes, however, into a state of delirium. The movements of the body become sluggish and feeble and the heart and the vasomotor apparatus are paralyzed. If large amounts of phosphorus reach the blood relatively rapidly, a direct paralysis of the heart may precede all other symptoms (*H. Meyer*).

The only efficacious *treatment of phosphorus poisoning* is the removal of the poison from the stomach or the attempt to render it harmless by securing its oxidation in the alimentary canal. Copper sulphate is the substance best adapted for this purpose, for not only does it cause emesis, but by its reduction the phosphorus is oxidized to phosphoric acid, and at the same time any phosphorus still unchanged combines with the reduced copper, forming an insoluble copper phosphide. Permanganate of potash also energetically oxidizes phosphorus, but ozonized turpentine which is recommended as an antidote is of doubtful value [and certainly cannot act on the phosphorus once it is absorbed.—Tr.].

Therapeutic Uses.—After phosphorus was discovered to be an important constituent of the brain and nerves, it was for a long time used with alleged great benefit in the treatment of different nervous disturbances. In view of the similar employment of arsenic, which, as will be seen below, acts in an entirely analogous fashion, which employment is still considered as justifiable, these older claims of the value of phosphorus in such conditions should not be dismissed offhand as erroneous.

Wegner's experiments have furnished a scientifically founded justification for the employment of phosphorus in *osteomalacia* and in *rickets,* as first recommended by *Kassowitz.* In particular, its curative effect in rhachitic children is not to be disputed, in which connection, it should be noted, that not only does formation of bone become normal again, but the other accompanying symptoms of rickets often disappear with surprising rapidity. All the same, the risks in prescribing phosphorus are not slight, for the rapidity with which it is absorbed from the alimentary canal and, consequently, the intensity of its effects, appear to be very variable and impossible to estimate. Doses of 1 mg. of phosphorus daily (two teaspoonfuls of phosphorus and cod-liver oil in the proportion 0.01 : 100), as ordinarily prescribed by pediatrists, are almost always borne without harm, but such doses taken for several days have also led to a fatal poisoning (*Nebelthau*). The attempt should, therefore, be made to abandon the therapeutic employment of phosphorus, replacing it by arsenic.

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ARSENIC

All arsenical combinations which are capable of reacting chemically are pharmacologically active, producing effects which in the last instance are due to the action of the anion AsO_3 or AsO_4. The organic arsenical compounds, such as cacodylic acid, $(CH_3)_2AsO_2H$, and arseniuretted hydrogen, AsH_3, however, first produce their own peculiar effects, the latter, for example, being very powerfully hæmolytic and in this fashion capable of producing fatal results. With the continuous administration of small quantities of such substances these characteristic actions are hardly apparent, but as a result of the formation from them of AsO_3 (*Heffter*) they gradually cause the typical effects of arsenic. The same holds true for atoxyl or sodium arsanilate (*Igersheimer*).

There is no evidence that either arsenous or arsenic acid forms any combination with any of the constituents of the protoplasm. Their solutions consequently, for the time being, produce no visible morphologic changes or functional effects in the nerves or other tissues. After a time, however, the poisoned cell dies and undergoes post-mortem changes. It is not known whether this is due to a catalytic inhibition of vitally important chemical reactions, or is due to a chemical reaction between arsenic and some constituent of the protoplasm, minimal amounts of which are necessary to the life of the cell. As ferments are not markedly influenced by arsenic, the catalytic effect does not, *a priori*, seem very probable (*Schäfer u. Böhm*). On the other hand, the possibility of a specific chemical combination between arsenic and some constituent of protoplasm is rendered improbable by *Bertrand's* statement that arsenic is an integral constituent of all living cells. This author found 1/200 mg. of arsenic in the hen's egg, chiefly in the yolk.

On Metabolism.—In its nature the action of arsenic on metabolism is essentially the same as that of phosphorus. In very small amounts it inhibits oxidation and exerts a favorable influence on growth and assimilation, causing a preponderance of assimilative processes as compared with those of dissimilation. The breeders of animals have long recognized this effect, and the so-called arsenic eaters in Steiermark look upon this as definitely established. The chemist, *Kopp,* observed that he gained 10 kilograms in weight during the course of two months in which he was working with arsenical substances (*Gies*). These practical experiences have been confirmed by exact observations on animals, in which the growth of normal animals was compared with that of those receiving arsenic, and by making exact analyses of the metabolism under the influence of arsenic (*Weiske*). In *Gies's* new-born rabbits of the same litter, to one of which arsenic had been administered daily, there was after four weeks a difference in weight of 30 per cent. in favor of the animal

fed with arsenic, which was also distinguished from its control by a shining pelt and a more abundant supply of fat in the subcutaneous tissues and in the peritoneal cavity. *The bones* of the arsenic animal were longer and thicker in the cortex, and the epiphyses consisted of thick, compact masses of bone such as result from the action of phosphorus (Fig. 46). Similar observations have been made in pigs and fowls, and, furthermore, the offspring of animals treated with arsenic were much stronger than those of the normal controls.

On Blood.—It is probable also that the formation of the red cells or the manufacture of hæmoglobin (*Delpeusch*) is stimulated by arsenic, but this has not been denitely proven (*Bettmann, Stockman;* see also Pharmacology of the Blood, p. 435).

Corresponding to this improvement of the assimilative processes, the nitrogen balance shows a retention of nitrogen, indicating in-

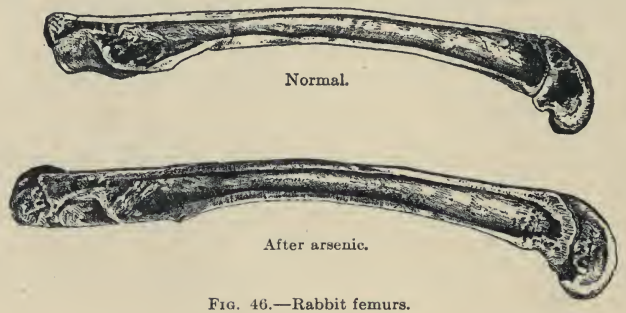

Fig. 46.—Rabbit femurs.

creased assimilation of proteid (*Weiske, Imjanitoff*). Nothing definite is known of the influence exerted on the total metabolism by small doses of arsenic.

It has been claimed that arsenic exerts a favorable influence on the development of infusoria (*Sand*), higher plants (*Zeller*, 1826), and yeasts, etc. (*Schultze*).

Toxic Effects.—Contrasted with the effects of small doses of arsenic in favoring assimilation and facilitating growth and regeneration are the opposite effects of large doses of arsenic, which cause an increased destruction of the tissues of the body and an inhibition of the functions of various organs. Among these effects are injury and abnormal destruction of the red cells (*Bettmann, Stierlin, Stockman, Charteris*) and as a result of this the development of jaundice, while the nitrogen balance indicates an increased destruction of proteids (*Gäthgens, Kossel, Imjanitoff*) and at the same time the respiratory exchange of gases is diminished (*Chittenden*). Fatty degeneration of the organs also ensues, lactic acid appears in the blood and in the urine, and the liver loses its power of forming glycogen (*Naunyn, Luchsinger, Konikoff*).

Combination of Assimilative and Disintegrative Actions.—Often, and perhaps as a rule, both of these effects of arsenic, the stimulation of growth and the destruction of the tissues, occur at the same time. Corresponding to the momentary resistance and vital powers of the different cells, and even more to the varying distribution of the poison in the different parts of the body, in one place the favorable building-up action preponderates, in another the destructive, while in still other situations no appreciable effect occurs.*

In chronic arsenical poisoning in the normal body those cells are especially affected which perform the larger portion of and the most complicated of the chemical reactions, particularly the cells of the liver, the kidney, the capillaries, and the blood. Certain pathological new growths, such as malignant lymphoma, syphilitic gummata, etc., appear to be especially susceptible to the dissimilative actions of arsenic. It is thus possible to produce such effects in many pathological growths without seriously or permanently injuring the patient himself.

Acute Poisoning.—Up to the present it is not possible to explain satisfactorily the therapeutic effects of this drug by our knowledge of the direct functional disturbances occurring in experimental acute arsenical poisoning. In poisoning of this type, frequently but not always, the symptomatic picture is dominated by two groups of symptoms which develop alongside of each other, one group being the result of depression, and, in more severe cases, of very acute paralysis of the central nervous system, while the other is due to the severe gastro-intestinal lesions. The former cause extreme lassitude, unconsciousness, and coma and failure of the respiration and circulation from paralysis of the respiratory and vasomotor centres, while the lesions in the alimentary canal, which also develop after subcutaneous or intravenous administration, cause violent pains, vomiting, and choleraic diarrhœa.

There appears to be a close connection between the gastro-intestinal disturbances and the disturbance of the circulation which develops at the same time and manifests itself by a pronounced fall in the arterial blood-pressure and a small, weak pulse. Experimental analysis of the circulatory failure has shown that, in addition to a weakening of the heart muscle, there is a diminution of the excitability of the vasomotor centres, and that finally the intestinal vessels no longer react to electric stimulation of the splanchnic nerves in the periphery. The contractile elements of the capillaries of the portal system are completely paralyzed, so that the blood accumulates and stagnates in them and their veins (*Pistorius, Heubner*). As a result of this capillary paralysis, there is a profuse transudation of serous

* The difference in effect is especially well evidenced in plants, those containing chlorophyll being especially susceptible to arsenic; of those containing none, the yeast fungus and many bacteria are very insusceptible, while the mycoderma oidium is entirely immune.

fluid into the intestines, whose epithelium, being here and there fattily degenerated, is raised up, and with the masses of the exudate may form a pseudo-membrane. A profuse watery diarrhœa results, the stools containing shreds of mucous membrane and at times blood.

As the mucous membrane of the intestine is directly injured as a result of the stasis, and probably in part also by the arsenic excreted through it, it is not able to resist the attacks of the bacteria to which it is constantly exposed, and parts of it succumb to a rapid destruction, so that ulcers may be formed (toxic autolysis). Necroses therefore are likely to be more extensive and severe in the large intestine than in the small intestine, which contains relatively few bacteria (*Cloëtta*).

Among the less direct effects are pronounced anæmia of all the other organs, anuria, asphyxia of the central nervous system, convulsions, and paralysis.

The central paralysis caused by arsenic is, however, not due to this interference with its blood supply, but to a direct toxic action of the drug. This is shown by the results of experiments on the frog, whose central nervous system is rapidly paralyzed from below upward when poisoned by arsenic, although it can support for hours an anæmia—for example, one caused by a standstill of the heart or by replacing the blood with normal NaCl solution.

The blood and lymph capillaries of the splanchnic system are more susceptible to arsenical poisoning than those in any other portion of the body, and in very acute poisonings are almost the only ones visibly affected.

In *chronic poisoning,* however, or when the drug is used medicinally for a considerable period of time, capillary paralysis and degeneration also occur, and often in fact chiefly in other mucous membranes and in the skin. This accounts for the conjunctivitis with œdema of the lids and for the angina, rhinitis, etc., and for the development of exanthemata resembling measles or scarlatina, as well as of herpes zoster, all of which are not infrequently observed under these conditions. Finally, arsenical melanosis, a brown pigmentation of the skin, resulting from chronic inflammation, may develop and last for months or years. The lesions of the peripheral nerves, polyneuritis, which may develop in chronic arsenical poisoning, are probably also to be attributed to a primary toxic action on the capillaries of the nerves.

Therapeutic Actions.—We have no exact knowledge of the extent to which curative effects of arsenic are due to such actions on the capillaries in the skin, the nervous system, and elsewhere. It is possible that this is of moment in the healing of the lesions of psoriasis. For the present, however, we have no explanation for the clinically well-established value of arsenic as a means of relieving neuralgias and many neuroses, such as chorea and asthma nervosa.

On the other hand, the already mentioned primary action of AsO_3 on metabolism, which, according to the individual susceptibility

or accessibility of the cells of the different organs, results in an acceleration of the growth or death and destruction of the cells, may be considered as a theoretical justication for prescribing arsenic in those cases in which the indication is either to improve the nutrition and growth of organs which are too feebly developed or to cause an absorption or destruction of pathological new growths or the destructions of parasities. Such are a poor state of general nutrition, cachexia, chlorosis, pathological disturbances of the growth of bones, such as ricketts or osteomalacia, in which last arsenic should be substituted for phosphorus, the action of which it is so much more difficult to estimate. Malignant lymphoma, pseudoleukæmia, syphilis, and some parasitic diseases are examples of the type of case in which the destructive effects are desired.

The ordinary doses range between 0.5 and 5.0 mg. of arsenic trioxide (arsenious acid), which may be administered in different preparations or in mineral waters containing arsenic.

In conclusion, the use of arsenic pastes to cause a local destruction or death of tissues should be mentioned. Their use is now almost entirely limited to their employment in dentistry for the purpose of killing the nerves in the roots of teeth, but formerly they were widely used as a means of destroying superficial epitheliomata.

The organic arsenical compounds have been found to be especially adapted to produce an etiotropic effect on parasites with the greatest degree of certainty and without essentially injuring the patient. Among such preparations *atoxyl* and *salvarsan* (see p. 535 ff.) are especially to be mentioned.

Excretion and Fat in the Body.—Arsenious acid is excreted from the body but slowly, and it would appear that it is never completely excreted. The lacteal glands are among the organs through which this excretion takes place, but after administration by mouth a considerable amount is excreted in the fæces, a smaller part, 4 to 14 per cent., appearing in the urine, while a very important remainder, varying from 20 to 80 per cent., is never excreted in any recognizable manner (*Hausmann, Heffter*). After subcutaneous injection, the same holds good, except that now the larger portion, from 10 to 19 per cent., is excreted in the urine, and the smaller part, from 3 to 4 per cent., in the fæces. A small part of the arsenic is absorbed by and retained in the hairs, and leaves the body in hairs and other epidermoid structures as they are cast off. Whether arsenic remains permanently in the body and in what form or place (perhaps in the bones?) is not known.

Tolerance.—If at first the arsenic be carefully administered in small doses, tolerance increases to such an extent that after a time doses may be borne without injury which would otherwise be certain to cause illness, and perhaps even as much as 3 or 4 times the usual lethal dose may be taken without harm. This has been observed

in the arsenic eaters of the Steiermark and has been confirmed by experiments on animals (*Hausmann*). [Clinical experience also indicates that a marked degree of tolerance is readily established.—Tr.]

Under these conditions the organism apparently retains larger amounts of the drug and possibly acquires a greater ability to form nontoxic organic combinations of arsenic. *Cloëtta,* however, claims that the tolerance is due to the fact that the absorption of arsenic from the alimentary canal decreases, the mucous membrane of the intestines becoming resistant and impermeable to it. Whether at the same time a general habituation of the cells to the specific action of arsenic also takes place has not been sufficiently investigated. With yeast-cells this appears to be the case, but in animals it is very doubtful. *Hausmann* found only that the mucous membranes of dogs which were accustomed to take arsenic were distinctly more resistant to the caustic action of As_2O_3 than were those of normal animals. *Cloëtta's* dogs, which had become habituated to arsenic, died a few hours after the subcutaneous injection of only one-sixtieth of the dose which for months past had been taken by mouth without injury.

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ANTIMONY AND ITS COMPOUNDS

In many regions antimonial preparations are, like arsenic, employed to improve the nutrition of cattle and to fatten them. As a matter of fact, the effects on the animal organism are qualitatively the same as those of arsenic, and differ from them only in degree and in the order in which the different effects occur. The same is true in regard to the effects on metabolism. In practice tartar emetic has been used in the same fashion as arsenic in the treatment of

psoriasis, but at present it is used almost exclusively as an emetic. [Antimonial preparations were formerly much used, especially in the treatment of pneumonia, to slow the heart and lower the blood-pressure. These effects appear to be due to a direct depressing toxic action on the heart muscle and to an action on the blood-vessels similar to that of arsenic. At the present time no one would think of using these drugs for such purposes.—Tr.].

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IRON

Iron and its compounds may also be looked upon as exerting a direct specific action on the metabolism. This is evidenced by their well-established influence on the formation of the blood-cells (see p. 440), as also by their "tonic action" in improving the general nutrition, which, although by no means definitely demonstrated, is generally accepted by clinicians. Moreover, its importance as an element essential to all plant life has been certainly established (*Molisch*), while *Fromme* has found that it favorably influences the growth of bacteria. Iron also appears to play a rôle in the activity of many enzymes (*Sacharoff*).

The toxic actions of iron resemble those of arsenic and antimony [but, owing to its slow absorption, they never occur except under laboratory conditions.—Tr.].

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MERCURY

It has long been known that patients undergoing a prolonged treatment with mercury often gain markedly in weight (*Liégeois*), and this has been confirmed by experiments on animals, in which, when very small doses of $HgCl_2$ are taken for a long time, growth is stimulated and the body weight increased, while the red blood-cells increase in number (for lit. see *Schlesinger*), even though in an experiment of but a few days' duration the metabolic balances may furnish no evidence of such effects.

In chronic mercurial poisoning or mercurial cachexia, we see the results of directly contrary actions,—namely, acceleration of cell decay and inhibition of oxidation. The severe nephritis, which develops almost immediately in acute mercurial poisoning, makes it impossible to demonstrate these effects by determination of the nitrogen balance as has been done for As_2O_3. However, the disappearance of glycogen, the appearance of lactic acid, and the fatty infiltration of the various organs indicate that qualitatively the toxic action is

essentially similar to that of arsenic. Mercurial poisoning, however, is differentiated from the latter by a more extensive destruction of the erythrocytes (*Kaufmann*) and by changes in the bones, which become poorer in lime salts and thinner and more brittle (*Prévost, Heilborn*).

Presumably this power of causing tissue degeneration is of essential importance in connection with the employment of mercury for the purpose of causing the rapid disappearance of syphilitic eruptions and new growths, which even when untreated show but slight tendency to persistence. It has been shown by *Justus* that mercury reaches the capillaries and permeates the cells of these lesions. Still more important, however, just as is the case with arsenical compounds, is the etiotropic action on the Spirochæta pallida (see p. 540).

Chronic mercurial poisoning may develop and lead to most disastrous results in patients undergoing long-continued mercurial treatment or in individuals working in certain occupations in which they are exposed to the danger of continual absorption of mercury. Among such are workers in quicksilver mines, in mirror and thermometer factories, etc.

As a rule, the first symptoms of chronic poisoning are similar to those of subacute poisoning,—salivation, stomatitis, and diarrhœa, to which are superadded very characteristic disturbances of the central nervous system. A condition of extreme psychic irritability, erethismus mercurialis, develops, and the patients become anxious and readily embarrassed or frightened, and not infrequently active mania may develop. A mercurial tremor of the muscles of the face and extremities develops, at first occurring only during voluntary movements but later occurring spontaneously and even during sleep. Finally, clonic convulsions may occur, which are occasionally accompanied by epileptiform attacks and hallucinations of hypochondriasis or other psychic disturbances. At the same time the nutrition is rapidly impaired and pronounced cachexia develops, and the patient becomes anæmic and the skin and muscles flabby. Not infrequently the jaw-bones undergo necrosis similar to that occurring in phosphorus poisoning.

Intercurrent diseases, most frequently phthisis, usually cause death when such conditions have developed. If, however, the patients are not too seriously poisoned and the absorption of the mercury is checked, by stopping its administration or by removing the patients from the mercurial environment, recovery may ensue after a time, but in some cases certain of the symptoms may persist indefinitely (*Kussmaul*).

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LECITHIN

In this connection it should be mentioned that, according to *Danilewsky,* frogs' eggs and larvæ grow and develop more rapidly under the influence of lecithin than under normal conditions. *Cronheim* and *Müller* assert that the addition of lecithin to the diet of nurslings is followed by an increased assimilation of proteid (also *Gilbert et Fournier, Slowtzoff*).

[Lest such statement should lead to an exaggerated idea of the value of the lecithin preparations, which are so widely exploited to the profession, the reader is reminded that lecithin is a constituent of many articles in our usual diet. The yolk of eggs, for example, contains it in large amounts.—Tr.].

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DRUGS AFFECTING CERTAIN PHASES OF METABOLISM

Thus far in this chapter the total metabolism has been discussed as if it were something without complexity, serving, as it were, as a general expression of the intensity of vital processes and growth of the cells of the body. Such a summary consideration is, however, no more and no less justifiable than is, for example, the general discussion of the narcosis of living cells. The essentialities of such a phenomenon may be observed, it is true, on all cells, whether differentiated or not, and may be considered from a general standpoint, but there exist in individual instances the greatest quantitative differences in these effects, corresponding to the chemical and functional differentiation of the different cells. The same holds true for the actions of the "metabolic drugs" thus far discussed, and already we have noted certain striking differences in the degree and manner in which the metabolism of different cells may be affected by different drugs. Such, for example, are the especially predominant actions exerted on the bones by such drugs as phosphorus, antimony, and arsenic, or by such internal secretions as those of the thyroid, the hypophysis, and the sexual glands, while the marked influence exerted by iron on the hæmatopoietic organs is another instance of such specialized action.

However, not only do the different types of cells exhibit such differences in their reactions to these various " metabolic drugs," but the different integral constituents of the cells also manifest similar differences in their reaction to them. It is, therefore, necessary

in this connection to consider more or less individually not only the cell as a whole, but also the organic energy-producing complex, as well as the catalyzers of the cells, their enzymes, their nuclear substances, and their mineral constituents.

However, right here we find our knowledge especially deficient, for, with the exception of a slight knowledge of the mineral metabolism of the cells, such, for example, as the action of Hg and of acidosis in removing Ca from the body and that of P and As in causing its assimilation (*Falta*), we know almost nothing about any regular orderly influencing of the special phases of metabolism by pharmacological agents.

CARBOHYDRATE METABOLISM

Diabetes Mellitus.—One of the most important of such disturbances of one phase of the metabolism is that which occasions a faulty utilization of the carbohydrates, whether this be due to the fact that the carbohydrates taken in the food or those formed from proteid are not stored up and retained in the form of glycogen and fat, or results from the inability of the actively functioning body cells to assimilate and utilize them as sources of energy. In either case the amount of the carbohydrates (usually glucose) present in the blood increases above the limit which can be kept back by the kidney, and consequently it is excreted in the urine without being utilized by the body. A discussion of the possible causes of these hyperglycæmic forms of diabetes is of no value for our present purposes, for it has not yet been possible to obtain any satisfactory and proven explanation of the manner in which these conditions may be influenced by drugs. Empirically it has been definitely established that the administration of certain drugs, alkalies, opium in large doses, jambul, and salicylic acid, lessens the excretion of sugar (*Kaufmann*).

According to *J. Rudisch*, the tolerance for carbohydrates is increased by atropine sulphate, as also by larger doses of the less poisonous atropine-methylium bromide (8 mg. t. i. d.). *Cavazzani* and *Soldaini* conclude from their experiments that atropine paralyzes those nerves in the liver which excite the formation of glycogen.

Toxic Glycosurias.—In poisoning due to many different agents, hyperglycæmic glycosuria occurs as a temporary symptom. Among these are all poisonings causing asphyxia, whether due to depression of the respiratory centre, such as is caused by narcotics, or to paralysis of the respiratory muscles, such as may be caused by curare, or to interference with the function of the hæmoglobin of supplying oxygen to the tissues, which may result from the actions of blood poisons, particularly carbon monoxide. That the asphyxia is the cause of all these glycosurias is proven by the fact that in these intoxications the glycosuria may be prevented by the free administration of oxygen wherever this may still be utilized, which evidently

is not the case in poisoning due to the "blood poisons" (for lit. see *Loewi*). Apparently such asphyxial glycosurias are essentially caused by a stimulation (by the asphyxial blood) of the " piqûre centre " in the medulla, for after section of the splanchnic nerves it does not occur.

The glycosuria which may be caused by caffeine should be mentioned in this place, for it, too, is prevented by section of the splanchnic nerves and is evidently due to direct stimulation of this " diabetes centre," which, like the other medullary centres, is directly stimulated by caffeine.

It would appear that glycosuria due to hyperglycæmia may also result from the asphyxial stimulation of a peripheral " hyperglycæmia-producing " mechanism, for in carbon monoxide poisoning glycosuria occurs even after section of the splanchnics.

Suprarenal Glycosuria.—Recent investigations have furnished a satisfactory explanation of the manner in which the stimulation of the diabetes centre produces a glycosuria. The subcutaneous and, under some conditions, the intravenous injection of epinephrin, the active principle of the suprarenal gland, causes a glycosuria of considerable intensity. *Waterman* and *Smith* have shown that the epinephrin content of the blood is increased after the piqûre glycosuricque, while *A. Meyer* has demonstrated that after extirpation of the suprarenals the piqûre does not cause glycosuria. It has also been shown that after extirpation of these glands or section of their nerves caffeine no longer causes an increase in the sugar content of the blood. It would therefore appear that, like the piqûre, all toxic stimulations of the diabetes centre produce glycosuria in the last instance by an action on the adrenals.

Phloridzin Glycosuria.—A glycosuria of entirely different type is caused by the internal, subcutaneous, or intravenous administration of phloridzin.* Its effect may be briefly stated to be the lowering of the renal threshold value for the excretion of sugar from the blood,—*i.e.*, its power of so altering conditions in the blood or the kidney that the kidney excretes sugar when the blood contains less than normal amounts. The nature of this change is not at all clear, but it is at least certain that it is a local change taking place in the kidney. Possibly it consists in an exaggeration of a normally practically imperceptible power of the renal parenchyma to form or split off sugar from some other substances or some sugar-containing compound normally present in the blood.

Other Types of Renal Glycosurias.—Glycosuria may also result from the administration of many poisons which, like uranium, the chromates, corrosive sublimate, and cantharidin, produce visible changes in the renal parenchyma. As in these glycosurias it has been shown that hyperglycæmia occurs only to a very slight degree

* A glucoside present in the bark of the roots of apple and cherry trees.

and by no means regularly,* it may be concluded that they are due to a diminished power of the kidney to prevent the passage of sugar from the blood into the urine.

Formation of Glycuronic Acid.—A quantitative alteration of the carbohydrate metabolism—namely, the increased excretion of the esters of glycuronic acid—results from the administration of a large number of different organic substances, among which are certain much-used drugs, such as chloral hydrate, phenol, camphor, many antipyretics, morphine, and others too numerous to mention.

Glycuronic acid is chemically very closely related to glucose, its relation being that of an acid to its corresponding alcohol, as shown by the accompanying formulæ:

$$COH(CHOH)_4COOH, \text{ glycuronic acid,}$$
$$COH(CHOH)_4CH_2OH, \text{ glucose.}$$

In the body it occurs only in organic combination, chiefly with some alcohol or with phenol. Under normal conditions very small quantities of it are formed, and are combined with such products of intestinal putrefaction as indol, phenol, etc., and are execreted in such combinations by the kidney. After administration of the above-mentioned substances, which in the body are reduced or oxidized to phenols or alcohols, the glycuronic acid is formed in increased amounts, or is not further combusted, as is perhaps normally the case, and consequently larger amounts are excreted in the urine organically combined with these substances. Glycuronic acid is probably not derived from carbohydrates already formed and present as such in the body, but, like glucose, is probably formed from certain mother substances contained in the proteid molecule, some of which are changed into glucose and others into glycuronic acid. The former is transformed into and stored up as glycogen, while the latter is instantaneously combusted unless it is protected therefrom by esterfication (*Fenyvessy*).

These combined glycuronic acids reduce alkaline copper solutions (as a rule, only if previously decomposed by boiling with acids) and are lævorotatory, although free glycuronic acid is dextrorotatory.

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Acidosis.—Many variations and disturbances may occur in the chemical decomposition of the tissues and food-stuffs, by which ordinarily the end products of metabolism are formed. While these variations from the normal at times produce hardly appreciable effects in the total energy balance, they may have results which are of great importance for the welfare of the organism. Thus, the formation and excretion of abnormal amounts of acids, which occur in poisoning by various agents, result only in a slight loss of energy, but, under some conditions, may so alter the chemical conditions throughout the whole body as to produce most serious results.

PURINE METABOLISM

The metabolism of the purines, pathological disturbances of which express themselves as gout, is of especial practical importance. Little is known of their causation, and consequently any successful treatment of these causes, in so far as this is actually possible, rests on no rational foundation. The first assumption naturally made, that the excretion of the uric acid retained in the tissues and in the blood could be hastened and increased by the administration of alkalies and other uric-acid solvents (piperazine, lysidine, etc.), has been found to be erroneous. While the salicylates increase the excretion of uric acid, they do not exert any material influence on the course of the disease (for lit. see *Ulrici* and *v. Noorden*).

Atophan.—The investigations of *Nicolaier* and *Dohrn* have shown that the excretion of uric acid is markedly increased by the administration of the different quinoline-carbonic acids and their derivatives. 2–Phenylquinoline–4 carbonic acid, to which the trade name of atophan has been given, possesses this power to an especially high degree. According to *Weintraud* and other clinical observers, very favorable results may be obtained in cases of gout by the administration for long periods of 0.5–1.0 gm. of this drug three or four times daily. Large quantities of alkaline waters should be drunk during this treatment, in order to prevent the deposition of uratic concretions in the kidney or bladder.

No drugs are known which have any power of influencing those anomalies of metabolism known as oxaluria and phosphaturia.

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CHAPTER XIII

PHARMACOLOGY OF THE MUSCLES

PHYSIOLOGY AND ANATOMY

There are three types of muscle-cells present in the body,—the striated or voluntary, the smooth or involuntary muscles, and the cardiac muscles, all differing from one another in their chemical composition, their histological structure, and their physiological functions.

The effects of pharmacological agents on the smooth and the cardiac muscles, the vegetative muscle, has been discussed in the chapters dealing with the pharmacology of the circulation and of the vegetative nervous system. Here a direct action on the muscles themselves could only very seldom be assumed with certainty, for, as a rule, the actions discussed affected the terminal nervous organs (nerve-endings) or the myoneural intermediary substance which does not actually belong to the integral substance of the muscle-cells, even though it does not degenerate after section of the nerves. In the case of certain pharmacological actions this was apparent from the peculiar effects of the drugs, which were explained by the character of the innervation, so that they expressed themselves, as in the case of epinephrin, sometimes as stimulation and sometimes as inhibition, while similar phenomena were also observed in connection with the actions of the group of "autonomic poisons." The only pharmacological substances which probably stimulate all the smooth muscle cells in the body are the substances of the digitalis group and the salts of barium.

The functional capacity of the striated muscles is, like that of the smooth muscles, dependent in general not only on the structure and chemical composition of their organic constituents,—proteids, lipoids, and carbohydrates,—but also on their inorganic constituents, especially the cations (*Höber*). Thus, *Overton* has shown that the excitability of muscles is entirely abolished when Na ions are withdrawn from them or from the fluid between their cells by æquimolecular sodium-free solutions, such as cane-sugar solutions, while *Loeb* has shown that it is tremendously increased by removal of the calcium ions. This latter is of toxicological interest in so far as the fibrillary muscle twitchings in poisoning by agents which precipitate calcium (oxalic and citric acids) may be attributed to the removal of calcium.

It is also certain that the water content of muscles distinctly influences their functional capacity (*Demoor et Philippson*), extreme dehydration having a marked effect, as will be shown. Probably

an abnormally large water content will also have a harmful effect. One of the ways in which this may be induced is by appropriate feeding, *Tsuboi* having found in rabbits, fed chiefly on potatoes, the water content of the muscles 2–7 per cent. higher and their hæmoglobin content 2–4 per cent. lower than that of normal controls.

The water content of muscle is diminished by work, the relative increase of the dry material being the most important factor in the hypertrophy resulting from work, except in the case of the cardiac muscles, which alone when hypertrophied show only a general increase in weight without any alteration in the proportion of their constituents (*Gerhartz*).

The voluntary muscles are the organs for motion and for production of heat. Their fibres are composed of the apparently homogeneous sarcoplasma and, imbedded therein, the anisotropic transversely striated fibrils. According to the relative amounts of these two elements (*Grützner*) or their reciprocal arrangement (*Paukul*), two types of muscle-fibres may be differentiated,—those richer in plasma, the so-called red muscles, which can remain contracted for long periods, and those containing less plasma, the so-called white muscles, which contract and relax quickly (*Ranvier, Erb*). The quickly acting elements are the anisotropic fibrils and the slowly acting the sarcoplasma (*Botazzi, Joteyko*).

These two elements appear to have entirely different chemico-physical properties and equally different physiological and pharmacological reactions. While the rapid twitchings of the fibrils are accompanied by an active production of heat and marked chemical changes, and accordingly relatively soon result in exhaustion,—that is, in the consumption of the readily available substances and the production of "fatigue substances,"—the slowly starting and persistent shortening of the sarcoplasma, which at times may last for hours or even weeks (as in contractures), appears to cause no measurable production of heat (*Brissaud*). It would appear, therefore, that this latter type of contraction represents only another physical state and normally exhibits none of the ordinary phenomena of fatigue. This is especially remarkable in persistent hysterical contractures.

Both these types of muscular contractions are under the control of the nervous system, and are without doubt governed by separate and distinct mechanisms, or at least by different stimuli, which in the case of voluntary movements are excited in the central nervous system and which may cause either short contractions or a more or less persistent contraction, depending on the character of the stimulus. The effective artificial stimuli are also different, the quick shocks of the induced current exciting the anisotropic fibrils, and the constant current the sarcoplasma.

Chemical stimulation of a nerve—as, for example, by concentrated salt solution applied to the nerve of a frog's muscle-nerve prepara-

tions—excites chiefly the persistent contraction of the sarcoplasma, to which may be superadded twitchings of the fibrillary substance, these being especially well developed if such twitchings are periodically induced by the induced current (Fig. 47) (*Limbourg*).

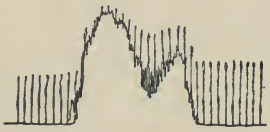

Fig. 47.—Nerve stimulation by KCl. Frog's gastrocnemius, electric stimulation every 10 seconds.

Direct and Indirect Pharmacological Actions.—From the above, it is clear that the functional activity of the muscles may be influenced by pharmacological agents acting either directly on the muscles or through the nervous system. As is well known, the ability of a muscle to contract depends almost entirely on the nervous impulses which are constantly reaching it, even when they cause no perceptible contractions. This is most strikingly shown by the much more rapid occurrence of rigor (either rigor mortis or that of toxic origin) in muscles with intact nerves than in those deprived of their nerves, or, what is essentially the same thing, in curarized muscles (*Kerry*).

It is, therefore, conceivable that, in conditions of purely muscular weakness or lessened functional power of the muscles, the strengthening of the reflex motor influences, or their facilitation by such drugs as strychnine or by electric stimulation of the motor nerves, may not only subjectively facilitate muscular action, but, by continuously keeping the nerve paths open (*Bahnung*), may also maintain and stimulate the chemical processes on which muscular contraction and activity depend (*Robertson*).

Contracture.—If a muscle becomes fatigued by continuous exertion or by maximal tetanic contraction, the excitability of the sarcoplasma—or, more correctly expressed, its tendency to shorten—is increased, the muscle passing into the well-known permanent shortening, *Tiegel's* contracture. In frogs, which at the end of the winter are in a state of malnutrition, this condition develops very readily, so that their muscles often, after a single powerful stimulation, contract and remain contracted for a considerable period. In myotonia congenita, or *Thompson's* disease, the muscles behave similarly, the muscle tone being absent during persistence of these contractures, as is also the case with hysterical contractures (*Herz*). In this condition also the sarcoplasma is not normal, exhibiting under the miscroscope an abnormal structure (*Schieferdecker*). An analogous disturbance is found in many other diseases of the muscles—*e.g.,* in pseudohypertrophic muscular paralysis (*Mendelsohn*) and in athetosis (*Kaiser*). This pathological condition may be induced by dehydration—by concentrated salt solutions or glycerin (*Santesson, Gregor*), as also by numerous poisons, but in an especially striking way by veratrine.

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VERATRINE

Veratrine (*Böhm*), obtained from the seeds of Veratrum sabadilla and V. viride, is a mixture of alkaloids of which cevadine (*Freund*) is the most important.

Locally it is very irritant to the sensory nerves, very small amounts being sufficient to cause sneezing, burning of the eyes, etc. When rubbed into the skin, it first causes a painful pricking and burning sensation and later **anæsthesia.** Veratrine ointment has, therefore, been successfully employed in trigeminal **neuralgia** and **sciatica.**

In connection with this action on the sensory nerve-endings it may be that this drug's action is not limited to these structures alone, for it must be admitted that it may possibly pass into and along the nerves and reach central portions of them, for *Joteyko* has made the remarkable observation that veratrine in the frog, unlike almost all other substances, can spread along in the nerves and relatively quickly transverse long stretches, even after complete stoppage of the circulation. This would explain the fact that, even after local application of this drug, paræsthesias occur at remote points (*Kunkel*), as well as the fact that, in animals poisoned by its subcutaneous administration, the characteristic alteration of the phenomena accompanying stimulation, which may be observed in the muscle after veratrine, may be also demonstrated in the electromotor phenomena occurring in the nerves (*Garten*).

Veratrine acts energetically on the **central nervous system,** causing vomiting, dyspnœa, and convulsions, and finally paralysis of the medullary centres.

Action on Voluntary Muscles.—The most thoroughly investigated action of veratrine is that on striated muscle, which in warm-blooded animals manifests itself by peculiar spastic and difficult movements, while in the frog this action is even more clearly developed.

If a frog be poisoned with a small amount (1/20 mg.) of veratrine, after a short time a characteristic alteration of its movements is noted, the frog springing quite normally, but then lying for a time stretched

out and only gradually becoming able to bend his legs again and to pull them up. The same muscular phenomena may be observed in nerve-muscle preparations, even after curarization; contractions induced by the induced current occur immediately, but either the muscle remains contracted or the contracted muscle after starting to relax promptly contracts again before it has completely relaxed and this time remains contracted for a considerable period (*Mostinzki*). If the stimuli follow each other rapidly, the contracture disappears, for the overexcitable sarcoplasma exhausts itself and breaks down, becoming under these conditions fatigued more quickly than the fibrillar substance, which ordinarily tires more readily (see Fig. 48).

The increased extent of the contractions and the augmented production of heat indicate that not only the sarcoplasma but also the

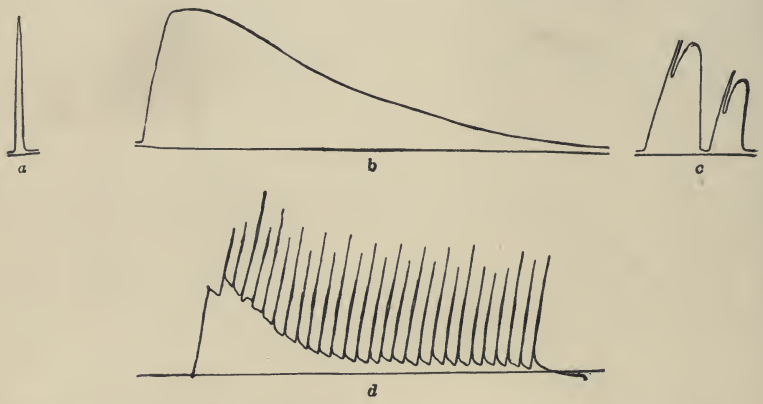

FIG. 48.—*a*, normal muscular contraction; *b*, *c*, veratrine contractions; *d*, influence of fatigue on veratrinized muscle.

fibrillar substance is rendered more excitable by veratrine, the total functional capacity of the muscle being increased, as was demonstrated by *Dreser*, using the frog's gastrocnemius.

Other Actions of Veratrine.—Veratrine exerts a similar action on the cardiac muscle, the contraction being prolonged, or, better expressed, passing off more slowly. By this action on the cardiac muscle the pulse may be markedly slowed, and, as a result of a depression of the centres for the regulation of the temperature, the temperature may fall after the administration of this drug, which formerly was extensively employed as an antipyretic. The action on the heart and the muscles might well be therapeutically useful were it not for the fact that these effects may usually be secured only by doses which produce a profound poisoning of the central nervous system and cause violent and dangerous disturbances of the circulation and respiration. It was formerly used in the dangerously large amounts of 0.05 gm. for single doses and 0.2 gm. per diem.

Veratrum viride and V. album contain *protoveratrine*, an alkaloid related to veratrine but much more dangerous (*Eden, Salzberger*).

Its actions differ considerably from those of veratrine, but no benefit is to be expected from its therapeutic employment.

[There is good ground for believing that veratrine slows the pulse in man as a result of central vagus stimulation rather than as a result of its typical action on the cardiac muscle. This drug is also used by competent authorities in the treatment of uræmia and of eclampsia, particularly when the blood-pressure is high. Under these conditions it often markedly lowers the blood-pressure. However, the weight of opinion appears to be against its employment for these indications.—Tr.]

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Strychnine.—*Paderi* states that the tone of a frog's gastrocnemius, isolated from the central nervous system, is augmented by very small doses of strychnine, the extent and duration of its contractions being increased, and that the same is true for the muscles of the frog's stomach. These observations appear to him to support the clinical employment of very small doses of this drug as a so-called "tonic."

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Of much greater practical importance than the above-described qualitative alteration of muscular action, produced by veratrine, is the causation by drugs of a *quantitative alteration of the functional capacity of the muscles*, as measured by the extent to which they can contract and by their absolute power,—*i.e.*, the largest weight they can lift.

MUSCULAR DEPRESSANTS

A diminution of their functional capacity, even to complete paralysis, is, as is well known, a symptom of many neuromuscular pathological conditions, and is usually associated with atrophy or degeneration of the muscles. Experimentally, also, such paralysis of the muscle-fibres may be produced, particularly in cold-blooded animals, by the administration of apomorphine or salts of Cu, Pb, or As (*Harnack*).

In chronic lead poisoning in man, a paralysis often occurs, especially in the extensors of the arm. Whether this be due primarily to changes in the muscle-cells or in their nerves or to degeneration in the cord is still uncertain.

The predisposition of the extensors of the arm to this affection is probably due to the greater use of these muscles, for in small children and in animals the paralysis caused by lead is atypical in its distribution, the lower extremities being affected as frequently as are the upper (*Stieglitz, Neumann, Edinger, Teleky*).

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MUSCULAR STIMULANTS

Caffeine and theobromine and, although in a different manner, alcohol may increase the working power of muscle.

CAFFEINE

In frogs—especially readily in R. temporaria (*Schmiedeberg*)—large doses of caffeine cause a maximal shortening and rigor of the muscles, which may be observed equally well in the muscles of the intact frog or under the microscope in teased muscle preparations at the moment of contact with a solution of caffeine. Rigor may also be induced in warm-blooded animals by injecting caffeine into an artery (*Lakur*).

With less pronounced caffeine action there is an increase in the muscle's irritability and ability to contract when stimulated, so that it not only responds to a slighter stimulus (*Paschkis*), but exhibits a *greater capacity for work and an increase in absolute power* (*Dreser*). Xanthine and creatin produce similar effects. In man also this drug increases the capacity for muscular work, as has been shown chiefly by exact ergographic investigations.

Muscular Fatigue.—Various parts of the neuromuscular apparatus are involved in the phenomena of fatigue, the intramuscular nerve-endings and the muscle-cells being primarily affected, and secondarily the psychomotor functions of the central nervous system (*Joteyko*). Both psychophysical investigations (*Kräpelin*) and the mathematical analysis of ergographic fatigue curves (*Henri*) indicate that the height of the lift is chiefly dependent on the condition of the peripheral neuromuscular organ, while the number of contractions which take place before complete exhaustion occurs depends on the condition of the motor centres. That is to say, in myogenic fatigue the height of the lift immediately or very quickly diminishes somewhat and then falls very gradually, while in central fatigue the height of the lift is at first normal but very rapidly falls to zero, so that the number of liftings accomplished is much less than is normally the case (Fig. 49).

Effect of Caffeine in Fatigue.—In fatigue, when the capacity for muscular work is already diminished, caffeine increases the total performance of muscular work. This is due chiefly to a direct beneficial action on the muscle-cells (*Mosso*), and to some extent to its favorable action on the central motor functions (*Kräpelin, Koch*).

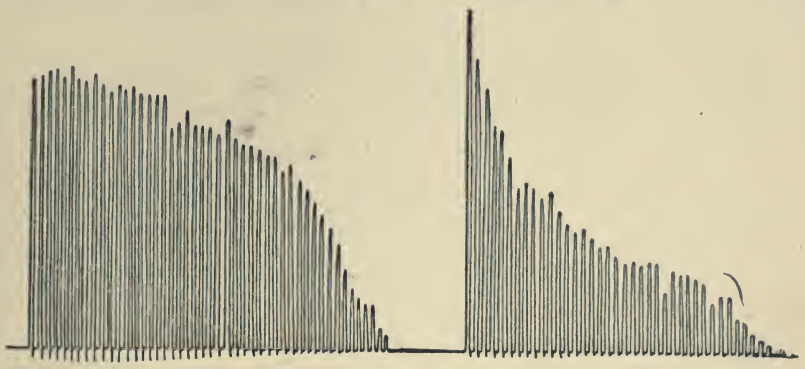

Fig. 49.—Ergographic curves.

These observations furnish a confirmation of the experience of mountain-climbers and soldiers, who long ago discovered the power of coffee, tea, etc., to overcome fatigue during exhausting exertion or marches. Creatin, which is a constituent of meat broths, influences the muscle function similarly to, though less powerfully than, caffeine.

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ALCOHOL

The action of alcohol on muscle function is much more complicated. That in man small amounts of alcohol (0.3–0.5 gm. per kilo. body weight) may under some conditions facilitate intense muscular activity and increase the power of performance is well known, but it is equally well known that they may produce a directly opposite effect. These effects result from the action of alcohol on the central nervous system and on the muscles and the nerve-endings.

Action through the Central Nervous System.—In a previous section (Pharmacology of the Central Nervous System) it has been shown that one of the early actions of alcohol is, on the one hand, to facilitate

the excitation of motor impulses and, on the other, to blunt the perception of sensory stimuli. Muscular activity may be favorably influenced both by the facilitation of the central psychomotor processes and by the more or less complete suppression of the fatigue reflexes resulting from muscular exertion (*Frey*).

Direct Action on Muscle.—Alcohol exerts two actions on the muscle itself which are antagonistic to each other. The capacity of the muscles for work and perhaps also their readiness to contract are, in warm-blooded animals, somewhat unfavorably influenced from the start, as shown by *W. Lombard* and by *Frey* for the flexors of the forearm in man.

Scheffer found that at first alcohol caused an increase of the excitability of the frog's nerve-muscle preparation, which did not occur with curarized preparations. *Verzas*, using somewhat longer dosage, obtained the same increase of excitability, even after curare, and an augmentation of functional power. These effects were produced both by methyl alcohol (1/80 of the body weight) and by ethyl alcohol (1/500–1/200 body weight). Larger doses had a harmful effect, which was less marked with methyl than with ethyl alcohol.

Normal curve. Alcohol curve.

Fig. 50.—Interval four seconds.

In spite of this, however, alcohol may increase the total performance of a muscle not by increasing the power or extent of the individual contractions, but by increasing the endurance of the muscle,—*i.e.*, increasing its ability to recuperate after each contraction. As a result of this action, exhaustion from continuous and therefore rapidly exhausting work is distinctly postponed. *Joteyko's* ergographic curves (Fig. 50) illustrate this well. In isometric tasks also the total performance is increased (*Hellsten*).

The increased recuperative capacity of muscles treated with alcohol is hardly susceptible of explanation except on the premise that *alcohol furnishes food and energy to the muscles.* This has been assumed by *Frey, Schnyder,* and *Joteyko,* and is confirmed by the mathematical analysis of *Durig's* experiments, in which he determined the effects of alcohol on the respiratory coefficient and the production of energy. If alcohol, which is readily oxidized to CO_2 and H_2O, is oxidized in place of other constituents of muscle, it is clear that there will be found smaller amounts of those decomposition products of the cellular material whose accumulation plays an important rôle in the causation of fatigue. The analysis of *Joteyko's* alcohol muscle curves speaks strongly for this view.

Joteyko sets up the following equation, $n = H + bt^2 - at^3 - ct$, as one constantly true for ergographic curves, in which n = the ordinate, the height of the lift; t = the abscissa, the interval of time; H = the height of the lift at the start, and a, b, and c are variables, a representing the formation of "fatigue substances," b the central motor facilitation, and c the consumption of the muscle's store of carbohydrates and reserve materials. With the use of this formula it may be shown that in the curves obtained under the influence of alcohol the value of a (*i.e.*, the formation of fatigue substances) is smaller than in normal curves.

A. Fick opposes the assumption that alcohol is combusted and supplies muscular energy, by objections based on mathematical calculations which indicate that in fatigue, as it occurs in ergographic experiments, no marked lessening of the supply of carbohydrate fuel can occur, and, therefore, there is no ground for concluding that muscular recuperation under the influences of alcohol is due to supplying the lacking fuel. The correctness of this criticism cannot be experimentally tested, for we do not know whether all the energy-supplying material in the muscles (carbohydrates) is equally readily available. Probably this is not the case, for it is possible to cause a complete disappearance of muscle glycogen only by extreme forced muscular contractions. This assumption is also rendered improbable by the marked diminution of the sugar in the blood which occurs during moderate muscular exertion at a time when the muscle certainly contains considerable glycogen (*Weiland*). Fick's critique could be equally well used to disprove the recuperative effects of small amounts of sugar (30 gm.) in extreme exhaustion. This latter has been certainly proved (*Schumberg, Joteyko*), and can hardly be explained otherwise than as the result of supplying energy.

Alcohol a Food in Case of Need.—From the above discussion it is justifiable to conclude that alcohol will cause no objective increase of the working power of strong and unexhausted muscle although bringing about a subjective facilitation, while in conditions of exhaustion it will positively increase the failing muscular power. It may, therefore, be useful as a promptly though temporarily acting means of recuperation and strengthening in case of marked exhaustion from work which must not be interrupted. Under such conditions it is for the time being more effective than sugar or other food, for, on account of its solubility in lipoids, it is very rapidly absorbed and taken up by all the cells.

Not a Complete Food.—Alcohol is, however, not a complete or even an approximately satisfactory substitute for food for muscle, for with larger doses, such as are necessary for the accomplishment of any considerable amount of work, its toxic action on the central nervous system becomes manifest and interferes with the power to work. Moreover, even with moderate not markedly toxic doses both *Chauveau* and *Durig* have shown that the utilization of the energy produced is not good: $\frac{\text{energy produced}}{\text{energy utilized}}$ being much less than when food containing no alcohol is taken. "With this fuel (alcohol) not only does the machine work more slowly than when the usual fuel (ordinary food) is used, but, when the attempt is made to use alcohol as fuel, the machine itself is for the time being damaged and, utilizing the available fuel uneconomically, performs less work than it should." It is not necessary to state that under certain conditions

the heat resulting from the combustion of alcohol may be of advantage to the body by sparing other fuel material.

The Rôle of Alcohol as a Food.—Not only does the oxidation of alcohol supply heat to the body, but it also supplies energy which may be directly utilized by various organs in the performance of their functions. The effects of alcohol on the isolated heart (p. 259) have indicated this with a high degree of probability. For the whole body this fundamentally important question has repeatedly been the subject of investigations,* in which the tissue and energy changes in man and beast at work and at rest have been observed. In these experiments the attempt has been made to determine whether the administration of alcohol results in a sparing of other constituents of the body, especially of the carbohydrates and fats and indirectly of the proteids.

Nearly all the authors who have occupied themselves with this question have concluded that alcohol, which is almost completely combusted in the body, may replace equivalent amounts of carbohydrates, fats, and proteids as a *source of energy.*

Kassowitz, in a careful critique of these articles, has shown that there is still reason to doubt the significance and interpretation of many of the results of such investigations, such as the calculations of the amount of CO_2 produced, of O_2 consumed, and of N excreted, as also of the directly determined caloric balances; but his critique based on such calculations can hardly be maintained to be satisfactory, in the face of *Durig's* experiments. Furthermore *Kassowitz* bases his denial of any nutritive properties of alcohol largely on theoretical hypothesis, as follows. He claims that the muscle-cell is not to be compared with a power machine run by heat resulting from the combustion of foodstuffs, but that, on the contrary, like all living cells, the muscle-cell is a labile complex, which is constantly being built up and broken down, assimilating the nutritive material brought to it and utilizing it to replace and build up anew its own protoplasm, producing heat and performing work by catabolism of its protoplasm and not by direct combustion of any sort of fuel which may be brought to it. As alcohol is not suitable material for these assimilative anabolic processes, it is useless, and is combusted in a sense outside of the protoplasm without utilization of the energy produced for the performance of work. It, therefore, cannot serve the cell as a source of energy as do the true foods, proteids, fats, and carbohydrates.

This argument against the biological utilization of alcohol can no longer be considered as pertinent, since it has been established that alcohol is formed in normal metabolism as a result of the anabolism of the protoplasm. *Stoklasa's* discovery, that animal and vegetable cells contained an enzyme which fermented carbohydrates with formation of CO_2 and alcohol, indicated with great probability that this was the case, although *A. Harden* and *Maclean* have since then raised a doubt as to the presence of such enzymes in animal tissues. *Landsberg* and *Reach,* however, have brought a direct proof of the presence of alcohol in normal tissues. The latter author found 0.0017 per cent. of free alcohol and small quantities of ethyl esters in rabbits' muscles, liver, and brain. As alcohol, therefore, is formed in the normal mechanism—*i.e.,* according to *Kassowitz,* "biologically"—it is no longer to be doubted that its combustion may be of value to the cell. Whether the alcohol reaches the cell from the outside or is formed in it can make no fundamental difference.

Alcohol, a Utilizable Food, with Limitations.—In general it may be said that alcohol is a food which is utilized rapidly, but that it

* For the very voluminous literature bearing on this subject, see *M. Kochmann* u. *W. Hall,* Pflüger's Archiv., vol. 127, p. 280.

is a poor food, to be used only in case of need, for the following reasons. Its potential energy is less economically utilized in the performance of work than is that of other food-stuffs, it cannot be stored up as a reserve to be used as need arises, but, under all circumstances, must be combusted at once, and, above all, it is poisonous. A slight degree, although not always a harmful one, of toxic action is produced whenever alcoholic beverages are used as stimulants or as food. In spite of this, it may often happen that, when other foods may not be administered,—as, for example, in septic febrile cases or in very sick diabetics to whom carbohydrates may not be given,—alcohol may be given with advantage, and may materially lessen the results of carbohydrate hunger, such as acidæmia and acetonuria (*Neubauer*).

Food and poison are not necessarily different things, for peptones and soaps when directly introduced into the blood are violent poisons. As, however, their chemical properties, their colloid nature, do not permit this, they are harmless food-stuffs when properly administered. If alcohol were to reach in proper amounts only the right place for its transformation, it would perhaps be quite as harmless as the higher alcohols, such as glycerin. Alcohol, however, differs from all such relatively harmless substances in its power of entering into solution with the lipoids. This property causes it to penetrate alike into all cells and to cause in them at least temporary disturbances of function. That this may lead to permanent serious results, especially to degenerative changes, is well known.

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TESTICULAR EXTRACTS

At the close of this section a very remarkable action of these extracts should be mentioned. This was first noted by *Brown Séquard* and his collaborators, and has recently been carefully in-

vestigated by *Zoth* and *Pregl.* According to these latter authors, the subcutaneous injection of Séquardine (a glycerin extract of bulls' testicles obtainable from Perrottet & Cie., Geneva) causes an extraordinary increase of the effect of systematic muscular exercise.

Daily injections for one week produced no effect on the muscular power as measured ergographically or otherwise, and daily exercises without injections were also without effect. Both together, however, caused a marked increase in the muscular power, showing itself in postponement of fatigue objectively and subjectively, as well as in an increase in the benefit resulting from pausing to rest. In *Zoth's* experiments, in which heavy dumb-bells were used daily and daily injections were administered, the increase amounted to 14–20 per cent. of the original performance after 8, 9, or 12 days, while without injections 70 practice exercises during five weeks caused an increase of but 12 per cent. Exercise plus injections resulted quickly in attaining an increase of power which by exercise alone was not attainable. A distinct increase in the circumference of the upper arm also accompanied the increase in muscular power.

These extracts appear therefore to bring about a peculiar improvement in the assimilative processes of the muscle-cells.

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CHAPTER XIV

PHARMACOLOGY OF THE BLOOD

Under pathological influences the blood may undergo both quantitative and qualitative alterations which demand not only dietetic but medicinal treatment.

Effects of Infusions on the Blood Volume.—The most important alteration of the blood volume, and one which often imperils life, is acute anæmia, a diminution of the blood volume resulting from hemorrhage or profuse diarrhœas (cholera) and affecting the whole vascular system, or in case of " bleeding into the abdominal vessels" as occurs in paralysis of the splanchnics, affecting chiefly the vitally important vascular systems of the heart and central nervous system. In such cases, merely increasing the volume of the circulating fluid by diluting the blood by intravenous—or in less urgent cases by subcutaneous [or rectal.—Tr.]—administration of physiological saline solution (0.9 per cent. NaCl) may be a life-saving measure. In such case the chief indication is to bring about more favorable conditions for the cardiac function (p. 319). In addition, according to *Ott,* the saline infusion actively stimulates the regeneration of the red cells. (See also *Zachrisson.*)

A condensation of the blood may, on the other hand, be of value under certain conditions, as, for example, for the purpose of favoring the absorption of pleural or peritoneal exudates or of œdema. This may be accomplished by bringing about the loss of large amounts of water through the skin, kidneys, or intestine. (See discussions of diaphoresis, diuresis, and catharsis.)

The most important anomalies of the blood are the alterations in the number and quality of the red and white cells which occur in chlorosis and other anæmias. In chlorosis the number of the red cells and their hæmoglobin content are markedly diminished. The indication is, therefore, to bring about a greater production of normal healthy cells, for which indication iron has been for centuries considered the most valuable drug.

IRON

Although originally the administration of iron in conditions of weakness, anæmia, and chlorosis was crudely empiric or else based on mystic ideas, it obtained a scientific foundation as early as 1746, when *Menghinis* discovered that iron was a characteristic constituent of the blood, existing " in sola sanguinis parte globulari." He also found that the administration of food containing iron increased the iron content of the blood. These observations, later confirmed by

numerous observers, were supplemented in 1830 by *Födisch*, who found the iron content of the blood of chlorotics to be materially diminished, and finally by *Andral, Gavaret,* and *Delafond* (1842), who demonstrated an increase in the number of the red cells after administration of iron. These quantitative observations have since then been repeatedly confirmed.

Older Theories as to Action of Iron.—From such observations it appeared that a scientifically founded and satisfactory theory for the effects of iron therapy had been obtained; that the iron which was administered was utilized in the formation of hæmoglobin. However, before long the correctness of this view was seriously questioned, chiefly for two reasons. Many clinicians cast doubt on the value of iron in the treatment of chlorosis, or assumed that the repeatedly demonstrated increase in the iron content, or in the hæmoglobin or in the number of erythrocytes of blood, which followed the administration of iron, even when other therapeutic procedures were not employed, was possibly not a real but only an apparent increase. As a matter of fact, up to this time the quantitative determinations of iron, hæmoglobin, and red cells had been made only in a given unit of blood, and, therefore, any increase found might be only a relative one due to concentration of the blood.

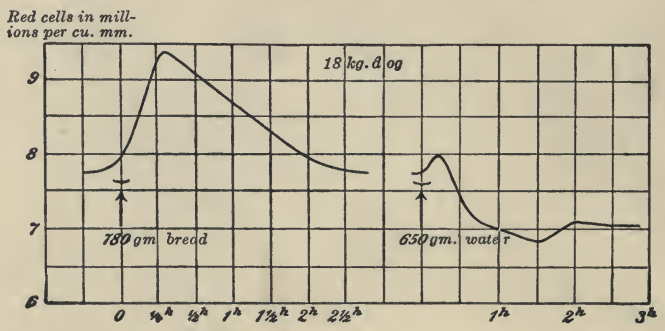

FIG. 51.—Graphic representation of variation in the number of red cells in the cu. mm. as a result of concentration and of dilution of the blood.

Marked variations in the concentration of the blood actually do occur under various conditions, either as a result of furnishing water to the tissues, especially to the glands, or as a result of vasoconstriction. The effect on the concentration of the blood exerted by the digestion of dry food—*i.e.*, by the pouring out of the digestive juices into the alimentary canal—is well shown by *Buntzen's* experiments on dogs (Fig. 51). Here feeding with bread increases the number of red cells in the unit volume by 10–20 per cent. In long-continued fasting also the relative number of red cells is markedly increased, for under these conditions the blood loses much more fluid from its plasma than from its cells (Fig. 52). This last observation has been confirmed in human subjects by *Andreesen.*

The effect of varying vascular tone is quite as well pronounced, with increased tone fluid passing from the blood to the tissues and the relative number of red cells rising, but falling with diminished tone. The vascular tone, as is well known, may be influenced through the vasomotor centres by

various means. For example, it is diminished by alcohol (Fig. 53) and increased by the action of cold,—*e.g.*, by cold baths (*Tönnissen*).

However, not every augmentation of arterial tone results in the passing out of plasma through the capillary wall, for, if the increased tone affects chiefly the smaller arteries and arterioles, the capillaries, being below the contraction, contain but moderate amounts of blood under low pressure, and therefore need not squeeze any plasma into the tissues. If, however, the tonic

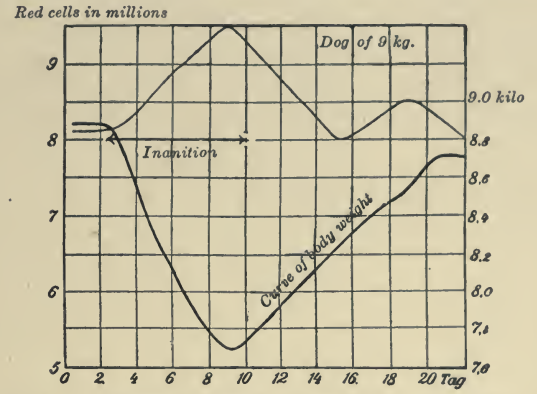

Fig. 52.—Influence of fasting on the concentration of the blood.

contraction affects principally the most peripheral capillaries or a portion of them (epinephrin intravenously), the blood stagnates in the less-contracted portions of the capillaries and arterioles lying above the constriction, and is there subjected to a high pressure which squeezes out the plasma fluid. In a similar fashion plasma is expressed in large quantities in artificial plethora, such as results from infusion of blood, although the vessels are not constricted. *Magnus* found that from 20 to 40 per cent. of the infused fluid was expressed

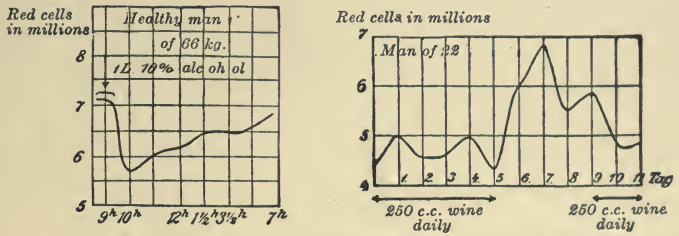

Fig. 53.—Influence of alcohol on concentration of blood (*Andreesen*).

into the tissues 3–5 minutes after infusion of homogeneous blood in amounts corresponding to 20–50 per cent. of their original blood volume. In such cases the blood was correspondingly concentrated.

One might be tempted to explain the variations in the relative number of blood-cells as being due not to a passing in and out of plasma through the walls of the finest capillaries, but by assuming an emigration of cells back and forth from reserves of concentrated blood, perhaps from the wide mesenteric veins, so that these variations would be explained as due only to an alteration in the distribution of blood containing varying numbers of red cells.

However, there are no grounds for assuming the existence of reserves of blood-cells, for the concentration of the red cells is almost equal in all veins and arteries (*Hess, Erb, Donath*).

These variations, however, which depend on administration of food or loss of water are not lasting, and cannot in any way explain the constant increase in the number of erythrocytes which results from the successful treatment of chlorosis.

Another series of objections to the view that iron medicinally administered is utilized for the formation of hæmoglobin base themselves on the physiology and toxicology of iron.

Iron in Food-stuffs.—In all food-stuffs, vegetable as well as animal, iron is present in assimilable form and in amounts sufficient to supply the increasing needs of the growing body and to compensate for the amounts lost by adult animals in the fæces and urine. It is present in these food-stuffs not in the form of salts, in which it may be directly demonstrated by ordinary reagents, but in organic combinations, probably in combination with nucleoproteids or similar substances. In this form the iron is without doubt absorbed and provides the body with the material for the formation and maintenance of its ferruginous constituents. With the exception of milk, rice, white bread, and many fruits, the substances used as food contain iron in such quantity that an ordinary mixed diet supplies enough iron for ordinary needs.

Iron Balance during Administration of Inorganic Iron.—If this be so, why not give anæmic cases an ample diet of food which is rich in iron, in place of administering iron salts, of which, to begin with, it was not known whether they were absorbed at all or, if absorbed, in what amounts? Formerly, in fact, it appeared very doubtful whether iron salts were absorbed at all, for in the human urine under normal conditions 1–2 mg. of iron are excreted daily, and after the administration of iron salts this amount is not increased, although in the case of almost all substances, which are absorbed and reach the circulation, at least a part is excreted in the urine (*Gottlieb*). As a matter of fact, almost all the iron thus administered may be recovered from the fæces (*Marfori, Kletzinski, Hamburger*).

This fact, however, was not a valid argument against the absorbability of iron combinations, for *Wild's* exact quantitative determinations of the iron content of different portions of the intestine have demonstrated that, of the iron contained in food which is certainly absorbed, any superfluous amount is excreted again in the lower bowel. Moreover, ordinary salts of iron when administered subcutaneously are excreted not by the kidneys, but exclusively by the intestine, as has been shown by *Gottlieb*. As the bile contains only traces of iron (*Novi*), this excretion must be the work of the intestinal glands. In view of these facts, it was not possible to deny that, when salts of iron were administered, they were absorbed in the upper portion and after circulating in the body were excreted in the lower portion of the intestine.

Finally, still another objection was raised by those doubting the value of iron medication, on the ground that, if corrosive effects be

excluded, neither chronic nor acute poisoning followed the oral administration of iron, although iron salts when administered subcutaneously or intravenously had proven themselves extremely toxic, similarly to arsenic (*Meyer* and *Williams*).

It was, therefore, concluded that, as ordinary food-stuffs contain sufficient iron, and as the medicinal preparations of iron are probably not absorbed and therefore cannot be utilized, the favorable effects of the administration of these preparations must be explained by local action in the alimentary tract, especially by a protection of the iron in the food from alteration by substances present in the bowel which have a strong affinity for iron, such, for example, as the sulphides.

These conclusions have, however, all been shown to be incorrect. The lack of toxicity of iron administered by mouth in no way indicates that it is not absorbed, for many substances,—*e.g.*, potassium salts, curare, and others,—although extremely toxic when administered intravenously or subcutaneously, are absorbed in large amounts from the intestine without producing any toxic effects. This is in many cases due to a protective influence of the liver, which is the first organ reached by these substances after they are absorbed, and which either renders them harmless by chemical means, or retains them for a time (*Rothberger*), so that their excretion by the kidney or intestine keeps pace with their arrival in the blood and thus prevents the attainment of that concentration in the blood necessary to cause toxic effects. This is also the case with the salts of iron.

Proofs of the Absorption of Inorganic Iron Salts.—In addition, it has been definitely proven that inorganic salts of iron may be absorbed in the absence of any lesions of the intestinal mucous membrane. That this occurs chiefly in the small intestine has been demonstrated both by microchemical examination of the intestinal mucous membrane (*MacCallum, Quincke, Gaule*) as also by the chemical demonstration of the presence of iron in the lymph from the thoracic duct 45 minutes after the introduction into the stomach of a 0.06 per cent. solution of ferric chloride (*Gaule*), and also by comparison of the amounts of iron administered to men and animals and the exactly determined amounts excreted by the intestine and the kidney (*Hofmann*).

Its Utilization in the Formation of Hæmoglobin.—Finally, *Kunkel* has shown that iron salts are not only absorbed, but that they are stored up in the body for future use and are used in the synthesis of hæmoglobin. This author repeatedly bled two puppies as nearly alike as possible and thus rendered them anæmic and impoverished in iron, feeding both animals exclusively on milk, which contains very little iron, except that one of the subjects received daily about 6 mg of Fe in the form of Liq. ferri albuminati. After six weeks one dog was extremely anæmic, its blood containing only 0.019 per cent.

Fe_2O_3, and the whole liver only 0.004 gm. Fe_2O_3, while the other dog, which had received the iron, was of normal strength, its blood containing 0.035 per cent. Fe_2O_3 and the liver 0.032 gm. Fe_2O_3.

These results were confirmed by *Cloëtta* in nine young puppies, which were subjected to experiment immediately after weaning. All of them received no food except milk, but six received in addition daily doses of 35 mg. of iron, as lactate of iron or as ferratin, a proteid containing iron in combination. The hæmoglobin was estimated at various intervals, with the results given in the table below.

Hæmoglobin in Growing Puppies Fed on Milk.

Hgb. expressed in percentages of normal Hgb. content	Group I, milk alone			Group II, milk and lactate of iron, 35 mg. Fe daily			Group III, milk and ferratin, 35 mg. Fe daily		
	1	2	3	1	2	3	1	2	3
After 4 weeks....	78	81	51	95	97	94	96	94	94
After 7 weeks....	66	67	31	92	95	93	95	93	91
After 9 weeks....	45	40	28	87	94	95	98	94	90
After 12 weeks....	35	..	24	..	99	94	99	..	93

Kunkel's results have been completely confirmed by *Abderhalden* working in *Bunge's* laboratory. In a large series of parallel observations, *Abderhalden* fed to young puppies as soon as weaned and to new-born guinea-pigs normal diet, or a diet containing little iron, and both of these diets with or without addition of iron, using in some cases salts of iron, and in others organic iron preparations such as hæmatin or similar substances. He found that all the iron preparations, when added to the diet containing little iron, were absorbed and used for the formation of hæmoglobin. When, however, iron preparations were added to the normal diet which contained iron, remarkable difference was noted between the animals which had received inorganic iron and those which had received organic iron. In the latter group no recognizable differences from the normal controls were noted, but the addition of inorganic iron preparations to the normal diet markedly stimulated both the formation of hæmoglobin and the gain in weight. These effects, however, were produced only for a certain length of time, after which habituation appeared to develop.

By these experiments, which have been substantially confirmed elsewhere (*Tartakowsky*), it may be considered as proven that the salts of iron may not only be utilized as material for the synthesis of hæmoglobin, but may also exert a specific action on the blood-forming organs (bone-marrow) and probably on the processes of growth and metabolism in other tissues. This latter is indicated by *Romberg's* observation, that in chlorosis the tissues contain abnormally large amounts of water and that this disappears under the influence of iron.

Finally, the histological findings in the bone-marrow agree with this assumption of a stimulation of the blood-forming organs by iron. According to *Fr. Müller,* the bone-marrow of animals artificially rendered anæmic contains more nucleated red cells when iron is administered than is the case when no iron is added to the normal diet.

It must therefore be assumed that the effects of iron in chlorosis are due to two factors: first, the utilization of the iron in the synthesis of hæmoglobin and in the formation of reserve substances which are rich in iron and are stored up in the liver; and, second, a specific stimulation of the cells which form hæmoglobin, as taught by *Trousseau* and as reaffirmed by *Harnack* and *v. Noorden.*

Relative Inefficiency of Organic Iron Preparations.—On account of the difficulty with which they are decomposed, hæmoglobin derivatives produce this second specific and therapeutically very important effect either not at all or in only a slight degree. Apparently they appear to be utilized only in the same way as the organic iron present in food-stuffs. [The same, in all probability, holds true for all of the high-priced and much-advertised preparations containing iron in organic combination. Although their vendors claim for them extraordinary therapeutic powers, they are without exception in all probability less effective than the old simple inorganic preparations. The only justifiable claim which may be made for them is that they do not produce the same local effects on the mucous membrane as do some of the inorganic preparations. This advantage is, however, purchased at the cost of therapeutic efficiency.—Tr.]

This power possessed by iron, of stimulating or causing metabolism and growth, is only a specific instance of its general importance for all vital processes. It is a constant and integral constituent not only of the lower animals (Crustaceæ, etc.), where it is present as ferrin, but it is necessary for the growth of the fungi (*Molisch*) and of the higher plants, in which latter it is necessary for the production of chlorophyll, although this contains no iron.

As exact experimentation and clinical experience both indicate that the action of the iron salts is materially different—at the least is quantitatively different—from that of the iron contained in food-stuffs, a rational foundation has been gained for the administration of iron in chlorosis in addition to providing for a diet rich in iron.

Moreover, the ordinary diet of man is by no means very rich in iron. *Stockman's* figures are as follows: Ordinary diet 8–11 mg. per diem; insufficient diets, especially when appetite is poor, 6–8 mg., and at times as low as 4 mg. In the daily output of fæces and urine of four exactly observed cases, he found that the iron approximately equalled the amount ingested. During fasting an adult man excretes 8–10 mg. of iron, for the celebrated faster *Cetti* the mean figure for the iron in the fæces was 7 mg., and for *Breithaupt* 8 mg. According to these figures, the normal human diet contains enough iron to replace

the unavoidable loss through wear and tear, but hardly enough to overcome any deficiency resulting from an existing disease. The importance of these facts is self-evident.

Comparative Value of the Different Iron Preparations.—From what has gone before, it may be concluded that, for purposes of practice, all iron preparations are in principle of equal value, with the exception of hæmoglobin, its derivatives, and similar organic combinations which in their behavior appear to resemble the iron contained in food. This has been confirmed by clinical experiments conducted for the purpose of investigating this assumption.

Behavior in the Alimentary Canal.—However, the different preparations differ quite materially in respect to their local actions on the mucous membrane of the alimentary canal and the rapidity and completeness with which they are absorbed. All the simple salts of iron, which possess an acid reaction, exert an astringent or corrosive action on mucous membranes, which varies in its intensity with the amount and the concentration. If the stomach be especially susceptible, this may be the cause of digestive disturbances or loss of appetite, and especially of constipation. Examples of such preparations are Ferrum reductum, converted into the chloride by the gastric juice, Ferri carbonas saccharatus, and the lactate, citrate, and malate of iron. By addition of alkali the acid reaction of the iron salts and their astringency are lessened. This accounts for the fact that such preparations as Blaud's pills are usually so well borne. The same is true of the chalybeate waters, which usually contain alkaline carbonates. Their great dilution also renders their local action practically negligible. Preparations containing iron in colloidal form or in combination with proteid, from which it is split off only gradually, are still less likely to produce undesirable local effects. Dialyzed iron and the albuminate or peptonate of iron are examples of such preparations.

Organic Iron Preparations.—**Ferratin** (acid albuminate of iron) containing 3 per cent. Fe, **carniferrin** (phosphocarnate of iron) 20 per cent. Fe, and **triferrin** (paranucleinate of iron) 30 per cent. Fe, all contain their iron in very firm combination, and, like the various commercial preparations, which contain hæmatin, produce no local effects, but also do not exert a specific stimulant effect after absorption.

In any iron preparations, ionizable iron gives with hæmatoxylin a dark-violet color-reaction. This may be used for determining whether or not the iron be present in available form (*Macallum*).

Ferric chloride is not only an astringent and irritant but also a coagulant for blood and possesses slight antiseptic powers.

Toxicology.—Actual poisoning by iron can occur only when iron salts are administered parenterally,—*i.e.,* subcutaneously or intravenously.

In rabbits, dogs, and cats, 30 mg. per kilo. body weight when thus administered cause paralysis and death. If the amount administered is so large that not all the iron can combine with the proteids of the blood, the free iron salts damage the kidney epithelium and are excreted by this organ, but such harmful effects never result from the subcutaneous administration of iron, sometimes employed in therapeusis (*Quincke, Lépine*). [One occasionally meets with statements that iron may in this way be harmful in cases of nephritis, but this view is in absolute contradiction to both experimental and clinical evidence.—Tr.]

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MANGANESE

Nothing certain is known concerning the influence on the blood exerted by this metal, but *Hannon* * claimed to have cured certain cases of chlorosis by its use, while other authors, among them *Cervello,* have made similar claims for lead and for copper.

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ARSENIC

It appears to be well established that arsenic exerts an action, very similar to that of iron, on the hæmatopoietic organs. This is

* *Hannon* attributed the good effects obtained by this drug to its power of protecting the food iron from the sulphides present in the intestine.

indicated not only by clinical evidence, but also by *Bettmann's* and *Stockmann's* findings in the bone-marrow of animals treated with arsenic. Thus far there is no scientific foundation for the use of arsenic in pernicious anæmia, leukæmia, and pseudoleukæmia.

HIGH ALTITUDES

A limitation of the oxygen supply affects the hæmatopoietic organs much as does iron or arsenic. It is well known that hemorrhage is followed by marked activity of the functions of the bone-marrow and by rapid regeneration of the blood. In fact, bloodletting has been employed in chlorosis as a means of exciting an apparently sluggish bone-marrow to greater activity. This, however, can be accomplished in a less harmful manner by cutting down the oxygen in the inspired air.

As early as 1877, *Paul Bert* expressed the opinion that in high altitudes the number of the red cells and the hæmoglobin must be increased in human beings or animals in order to make it possible for them to obtain sufficient oxygen from the rarefied air. *Viault* in 1890 confirmed this view completely by observations made on himself and a companion during a three weeks' stay at an altitude of over 4000 metres. He found the red cells increased from 5 to 7½ or 8 million per cu. mm. Analogous observations have since then been made by numerous others, especially by *Egger* and by *Miescher* and his pupils (see Fig. 54).

Further investigations have shown that this result is due to the diminution of the oxygen in the air, for the same increase in the number of the erythrocytes results from long-continued breathing of rarefied air (*Schaumann*), or air from which part of the oxygen has been removed (*Sellier*).

For a time it was uncertain whether this increase of the red cells was relative or absolute,—*i.e.*, whether the blood on account of loss of plasma appeared to contain more cells or whether the amount of

Author	Animal	Height in m.	Hæmogl. per kg.	Air diluted to correspond with altitude of—	Hæmogl. per kg.	Diff. in per cent.
Jaquet u. Suter	Rabbit	280	5.39	1800 m.	6.59	+23.0
Jaquet.....	Rabbit	280	5.50	1600 m.	6.73	+20.0
Abderhalden.....	Rabbit	280	7.99	1800 m.	9.32	+16.6
Abderhalden.....	Rat	280	8.92	1800 m.	10.62	+19.0
Zuntz.....	Dog	400	10.78	2150 m.	13.00	+20.0

plasma remained constant while abnormally large numbers of red cells were produced. This was settled by determining the total hæmoglobin content of animals which had been kept in atmospheres containing different amounts of oxygen, due allowance being made for

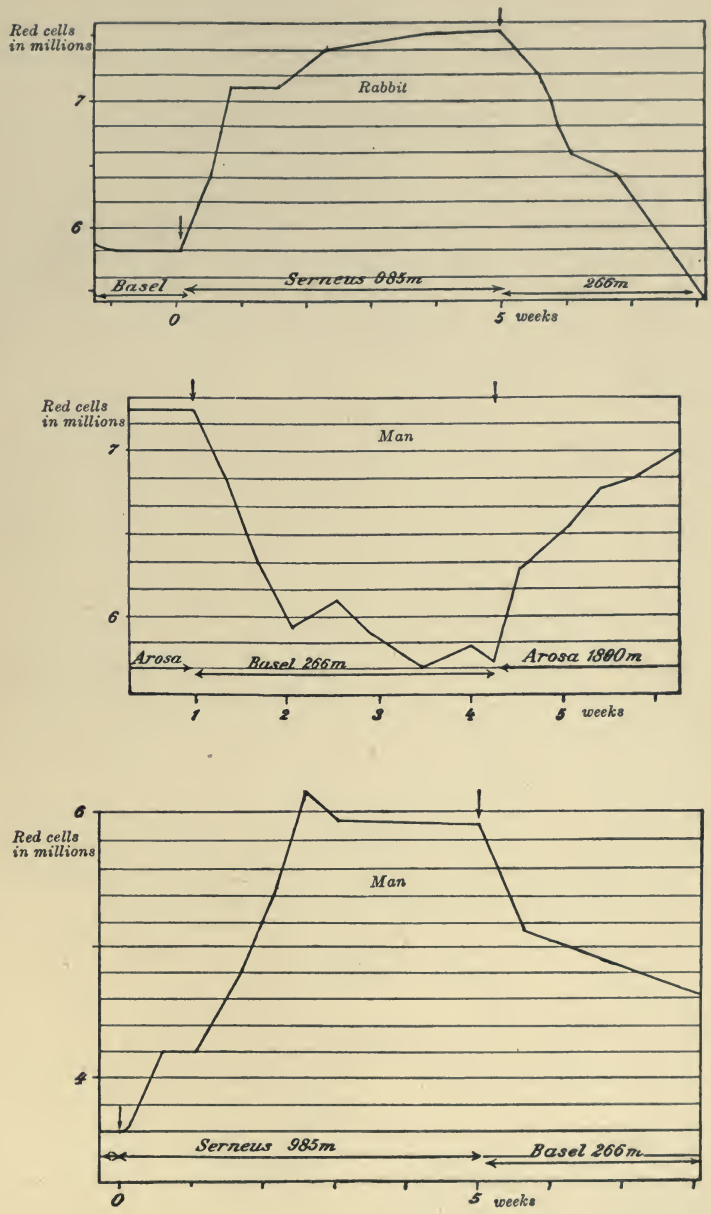

FIG. 54.—Effect of various altitudes on the number of the erythrocytes.

variations in body weight. The results of such investigation as shown in the preceding figures demonstrate with certainty an actual increase in the number of the red cells. This is also indicated by the histological examination of the blood and bone-marrow of the animals kept at high altitudes, which demonstrate the presence of numerous normoblasts in the blood, and by the redness of the bone-marrow.

Recently *Douglas*, using *Haldane's* method for determining the total hæmoglobin, questions these conclusions, but this method, according to *Dreyer* and *Ray*, is not reliable, and therefore his objections cannot be considered as proven.

This increased production of blood-cells and hæmoglobin under the influence of diminished oxygen tension,—*i.e.*, of very slightly deficient supply of oxygen—is to be considered as an unusually delicate compensatory and regulative reaction of the hæmoglobin-producing organs, especially the bone-marrow.

This new formation of red cells is, however, not demonstrable until the rarefied air has been acting on the subject for several days, but the number of cells to the cu. mm. is at once distinctly increased, as a result of a temporary concentration of the blood in the cutaneous vessels, due probably to an alteration in the distribution of the blood throughout the body.

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Polycythæmia, or erythrocythæmia, is a condition practically the opposite to chlorosis and one due to unknown causes. As far as is known, pharmacological agents exert no influence upon it, but repeated bloodlettings at times give passing subjective and objective relief.

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LEUCOCYTES

Up to the present time, there is no satisfactory explanation of the manner in which pharmacological agents influence the leucocytes. While the number of these cells present in the blood at the surface of the body may be influenced by the distribution of the blood in different parts of the body (*Bohlandt*), increased formation or an increased emigration into the blood from the organs in which they are formed may cause an increase in their number. Thus, the leucocytosis caused by pilocarpine is the result of the contraction of the

smooth muscles in the spleen and the lymphatic glands squeezing lymphocytes into the blood, for after ligature of the splenic vessels this drug does not alter the number of the leucocytes (*Harvey*). Action on the lymphatic elements of the intestine is the probable cause of the leucocytosis appearing during the increased activity and hyperæmia during digestion, as also for that caused by bitters and other numerous drugs which stimulate or irritate the alimentary mucous membrane (*Pohl*).

Quinine and salicylic acid both possess a specific action on the leucocytes, their movements being inhibited even by very dilute solutions, while concentrated solutions kill them (*Binz*).

The distribution of the leucocytes throughout the circulation is influenced by chemotactic substances, and their number may be affected in an indirect manner by numerous drugs. Thus, the application of irritants to the skin is followed at first by hypoleucocytosis, later by hyperleucocytosis (*Winternitz*). According to *Hamburger* and *de Haan*, lime salts specifically augment the motility and phagocytic power of the leucocytes.

Finally, the leucocytes may be destroyed in the circulating blood, for they are labile elements prone to destruction and succumb to the action of many destructive factors (see Metabolism). Thus, they are destroyed by X-rays, and in leukæmia the spleen diminishes in size (*Linser*). [**Benzol** has recently been shown to greatly diminish the number of leucocytes in leukæmia.—Tr.]

On the other hand, the destruction of the red cells by specific poisons is accompanied by a hyperleucocytosis, due both to increased production of the white cells and to their being swept into the blood from the tissues (*Heinz*).

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COAGULABILITY

Among the changes which take place in the unformed elements of the blood, its coagulability is one which may be influenced by pharmacological agents,—*e.g.*, in obstinate bleeding, purpura hæmorrhagica, hæmophilia (?).

According to practical experiences, the administration of **lime salts** favors the formation of firm clots,* while *Reverdin* claims similar ef-

* [Doubt has been thrown upon this claim by *Cole* and others who have failed to note that such increase in the coagulability of the blood followed the administration of lime in various forms or that of gelatine. There is also a difference of opinion among clinicians as to this matter, which certainly needs further investigation.—Tr.]

fects from Glauber's salt by mouth or intravenously, and *v. d. Velden* claims the same results for large injections of NaCl solutions. **Gelatin** (15–20 gm. daily) internally or subcutaneously is stated to stop or lessen capillary bleeding (*A. Bass*). This may be done only to the lime which is present in the gelatin in the amount of 0.6 per cent. (*Zibell*). [It should not be forgotten that cases of tetanus have been caused by the injection of insufficiently sterilized solutions.—Tr.]

[**Epinephrin**, when injected intravenously or subcutaneously into experimental animals, often causes an annoying increase in the coagulability of the blood. It is possible that this also occurs in man, and it may be that the favorable effects claimed from the use of this drug in hemorrhage from inaccessible points is due to such action.—Tr.]

The diminution or abolition of the coagulability of the blood will probably never be therapeutically indicated unless to prevent threatening or progressive venous thrombosis, but in many experiments in animals such action may be desirable.

Sodium oxalate or citrate (1 to 100), when added to the blood, by combining with its calcium prevents coagulation. However, these salts (or the deprivation of calcium) are toxic for the heart and the nervous system, and therefore they cannot be used in living animals, but only in experiments where surviving organs are perfused. [Here, too, their value is very doubtful.—Tr.] On the other hand, the glands of the leech contain a substance which is harmless when injected and which for a time prevents coagulation (*Haycraft*). *Franz* and *Jacoby* have named this substance hirudin. In the purest form in which they were able to obtain it, it appeared to be deutero-albumose. One milligramme of it will permanently prevent the coagulation of 20 c.c. of rabbit's blood.

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VISCOSITY

In recent years considerable attention has been paid to the viscosity,—*i.e.*, to the internal friction—of the blood in physiological and pathological conditions (*Kramer*), and attempts have been made to find drugs or other agents which will lessen the viscosity and thus facilitate the circulation of the blood.

As first claimed by *Poiseuille* and confirmed by *Müller* and *Inada* and by *Kottmann*, potassium iodide appears to produce this effect, and recently there is a tendency to attribute to such action the beneficial effects which follow the use of this drug in arteriosclerosis.* The diminished viscosity resulting from the administration of this drug is not due to any alteration of the plasma, but is probably the result

* [See J. of A. M. A., 1912, for *résumé* of the literature.—Tr.]

of alteration of the red cells. Mere changes in the volume of the red cells markedly influence the viscosity of the blood, so that the introduction of CO_2 into the blood, which augments the volume of these cells, markedly increases the viscosity. For this reason in asphyxia the viscosity of the blood is much increased. [The practical importance of this effect of CO_2 in increasing the viscosity of the blood has not been sufficiently appreciated by the general medical profession. In cases with even moderate cyanosis, marked relief may be given to a struggling heart by any measures which will relieve this condition. In view of the general skepticism as to the value of oxygen inhalations, these facts should not be forgotten.—Tr.]

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Alterations in the Chemical Composition of the Plasma.—Under certain conditions it may be desirable to bring about an alteration of the inorganic elements of the plasma,—that is, to introduce certain salts which appear to be lacking. In these cases, however, the alteration or pathological composition is not confined to the blood alone, but affects all the tissue fluids and to some degree the tissues themselves, including the red cells, in so far as the ions in question are able to permeate them. An example of such procedure is perhaps to be found in the administration to scorbutic patients of the salts of the vegetable acids and potassium, but this therapy rests on a mere assumption for which there is no real scientific basis. There is no doubt, however, that such is the explanation of the benefits resulting from the addition of NaCl to diets composed entirely or chiefly of vegetable food, for with such diet large amounts of potassium salts pass through the body and, by mass action, compel the excretion of its sodium salts (*Bunge*). (See Salt Action, p. 388.)

Alkalinity.—In conclusion, mention should be made of diminished alkalinity of the blood, a very important condition and one often amenable to therapeutic measures. Evidently it is always merely one expression or symptom of a general metabolic disturbance, in which abnormal amounts of acids (lactic acid, oxybutyric acid, and others) accumulate in the body. (See Pharm. of Metabolism, p. 389.)

TOXICOLOGY OF THE BLOOD

In addition to the various therapeutically useful agencies by which the composition of the blood may be influenced, there are a number of others which are always harmful and may thus be termed blood poisons. Of these the more important will be considered.

CO, CARBON MONOXIDE, the chief poisonous constituent of coal-gas and illuminating gas, has an affinity for hæmoglobin about 200 times as strong as has oxygen. Therefore, when present in the atmosphere in a concentration only 1/200 of that of oxygen,—*i.e.*, in a proportion of 1 to 1000 by volume,—it is able to replace one-half of the oxygen in the hæmoglobin, and in higher concentrations to replace it almost entirely.

By use of the following equation, it is possible to calculate the extent to which a given amount of CO will replace the oxygen in blood at body temperature (*Hüfner*),

$$x = \frac{100}{0.006518 \cdot \frac{Vo}{Vc} + 1}$$

If Vo = percentage of O_2 in the air and Vc = percentage of CO, then x = the percentage of the hæmoglobin which will combine with CO.

If, for example, the air contains 21 per cent. O_2 and 0.1 per cent. CO,

$$x = \frac{100}{0.006518 \cdot \frac{21}{0.1} + 1} = \frac{100}{2.3688} = 42.21 \text{ per cent.}$$

i.e., under these conditions nearly one-half of the blood would be saturated with CO if the subject remained in such an atmosphere sufficiently long.

If the air contain 0.3 per cent. CO, $x = 68.7$ per cent., and human beings cannot survive such conditions, for in them death results when 60–70 per cent. of their hæmoglobin is saturated with CO. In birds, with their higher temperature, 50–60 per cent. CO saturation of the blood is fatal, but rabbits survive up to nearly 80–90 per cent. (*Dreser, Hüfner*). If the supply of CO ceases (before death ensues), or, otherwise expressed, if its concentration in the air sinks to zero, it is gradually driven out from the blood by the pure air breathed in, and the larger the amounts of oxygen in the air the more rapidly does this occur. The recovery from poisoning by carbon monoxide is, therefore, materially accelerated when pure oxygen is inhaled. [Direct arm-to-arm transfusion of blood is also doubtless a life-saving procedure in such cases, and in extremely grave cases should, when feasible, be employed.—TR.]

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HYDROCYANIC ACID.—In poisoning by this acid, which kills by rapid paralysis of the respiratory centre, the blood also is affected, the absorption of oxygen by the oxidizable elements of the body cells being interfered with or prevented, just as other so-called catalytic processes are inhibited by HCN (*Gaehtgens, Geppert*). For this reason, the venous blood has almost the same color and O_2 content as arterial blood. Methæmoglobin resulting from decompo-

sition or other processes forms with cyanides a bright red combination, cyanhæmoglobin, which at times renders possible the recognition of cyanides as the cause of death (*Kobert, v. Zeynek*).

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METHÆMOGLOBIN *is formed from oxyhæmoglobin by the action of a large number of substances.* This is a combination of oxygen and hæmoglobin, in which the oxygen is so firmly combined that it is not available for the internal respiration of the tissues. Such blood is of a reddish-brown or in extreme cases of a coffee color. By reducing agents, methæmoglobin is changed to normal hæmoglobin, and in this way the reducing substances present in normal blood may transform small amounts of methæmoglobin to hæmoglobin, otherwise cells thus affected disintegrate and the coloring matter dissolves in the blood, which may cause serious results, such as methæmoglobinuria, blocking of the uriniferous tubules, and uræmia.

Of the substances which thus affect the red cells the most important are the *chlorates, nitrites,* and *aniline* and some of its derivatives, especially *acetanilide.* [Many of the salicylates and other antipyretics produce analogous changes in the blood to a less degree, but still to an extent which may under certain conditions prove of practical significance (see p. 478). The sulphones, sulphonal, trional, and tetronal form from hæmoglobin a pigment, hæmatoporphyrin, which is excreted in the urine. Pyrogallol, much used in photography, should also be mentioned in this connection.—TR.]

HÆMOLYSIS

Hæmolysis,—*i.e.,* a dissolving of the red cells of the plasma—occurs if the osmotic tension of the blood sinks appreciably below that of these cells. This occurs, for example, if the blood be markedly diluted by the infusion of pure water. If under special conditions the osmotic tension of the corpuscles has been markedly increased over that of the plasma, this, too, results in hæmolysis. Such may be the case if the blood has been strongly concentrated in some portion of the body by the injection into the tissues of substances which strongly attract water,—*e.g.,* concentrated salt solutions or glycerin. (This occurs especially if stasis exists.) If then the distended hypertonic red cells pass with the blood into other portions of the body where the plasma is of normal tension, they undergo hæmolysis (*Filehne*).

A hæmolytic action is also produced by all substances which chemically or physicochemically attack any integral components of the

corpuscular stroma and thus destroy the balance of the normal protoplasmic combinations. *Saponin,* on account of its strong affinity to cholesterin, exerts this action (*Ransom*), as do ether, chloroform, and all the narcotics of this group, by virtue of their affinity to the lecithin present in the red cells. From a practical stand-point these toxic actions are of no moment, for saponin cannot pass unchanged through the mucous membrane of the alimentary tract and the narcotics do not attain a sufficient concentration in the blood. [Repeated administrations of chloroform, and probably also of ether, do cause a distinct anæmia, probably due to this cause, and in the rabbit such hæmolysis due to ether is frequently observed.—Tr.] The hæmolysin contained in Morchella esculenta (*Böhm*), an edible mushroom, which is readily absorbed from the stomach into the blood, is practically important. It is removed from the fresh mushrooms by boiling with water and appears to be destroyed by drying. It is not known which component of the corpuscles it combines with. The same is true of AsH_3, which hæmolyzes the blood-cells when inhaled in even very small quantities.

Finally, the *hæmolytic toxins,* such as those in snake venoms,—*e.g.,* in cobra venom [and hæmolysins formed by bacterial action.—Tr.],—should be mentioned, as also hæmolysis by heterogeneous sera.

The effects of hæmolysis are very varied. In case of very extensive and rapid dissolution of the blood, the setting free of fibrin-ferment may cause clotting in the vessels, with fatal results. With less marked hæmolysis the abnormal amount of dissolved hæmoglobin causes an abnormally large production of bile-pigments and jaundice, while that portion of the hæmoglobin which is not retained by the liver and spleen is excreted by the kidneys, where it may block the uriniferous tubules and cause anuria.

In hæmolysis not only the coloring matter of the blood-cells but also their lipoids (lecithin, etc.) and salts enter the plasma. If, as is the case in many species, the erythrocytes contain large amounts of potassium salts, these may fatally poison the heart. The liberated lipoids, if derived from the cells of the same species, are relatively harmless, but the heterogeneous ones are extraordinarily poisonous. Rabbit's blood injected intravenously into a dog is hæmolyzed by the dog's plasma, and the liberated lipoids quickly paralyze the respiration and the central nervous system (*Gottlieb u. Lefmann*). It is these poisonous components of the dissolved red cells which are responsible for the dangerous effects of the transfusion of heterogeneous blood, which, when hæmolyzed, at once becomes very poisonous.

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CHAPTER XV

PHARMACOLOGY OF HEAT REGULATION

ANTIPYRETICS

All the drugs which exert an influence on the temperature act much more strongly on febrile than on normal temperature. However, fundamental differences in their action on the normal and on the diseased organism exist only in those antipyretics which, like quinine in malaria, exert a direct influence on the cause of the fever (see Etiotropic Agents, p. 527), while the great majority of the drugs of this group exert their influence only on the symptom of increased temperature. That even these purely symptomatically active antipyretics lower the temperature of febrile individuals so much more markedly than they do that of the healthy is due to the different behavior of the heat-regulating mechanism in health and in fever.

THE HEAT-REGULATING MECHANISM

The heat-regulating mechanism includes all those processes taken as a whole by which the body temperature is maintained constant in spite of the changing temperature of its environment. In the cold-blooded animals, in which there is no heat regulation, the production of heat and the body temperature rise and fall with the external temperature, but in the warm-blooded animals heat and cold are effective stimuli for a number of physiological processes, whose protecting influence enables the organism to maintain its own proper temperature in spite of a lowering or raising of the external temperature. These processes are in part local ones, which occur in the cooled or warmed surface of the body, and in part are the results of complicated remote actions induced reflexly.

By the local action of cold, the cutaneous vessels are constricted in those regions of the skin which are affected, and the skin becomes anæmic, pale, and cold (*F. Frank, Mosso*), and, as the skin with its cushion of subcutaneous fat is a poor conductor of heat, it acts as a protecting cover to the internal organs. On the other hand, heat causes local relaxation of the cutaneous vessels and consequently redness and a freer flow of blood to the skin. Here these effects are at least in part due to a direct action of cold and heat on the vessel walls, for even the vessels of a surviving organ which has been isolated from the central nervous system dilate under the influence of heat and contract under that of cold (*Lewaschew, Bernstein, Langendorff*).

Cold, however, acts not only on the vessels of that portion of the

skin which is directly exposed to it, but also on its temperature nerves, and, as a result, there is a subjective feeling of cold, for only when the skin is poorly supplied with blood and is itself cool do we feel cold. Cold also excites reflexes which limit the loss of heat by the body and increase its production.

This limitation of the heat output is brought about by a reflexly induced constriction of all the cutaneous vessels, not only in the parts directly exposed to the cold but also over the whole surface of the body, which becomes pale and anæmic, and consequently a general feeling of cold may be produced by the cooling of only one part of the body. Such reflexes may be especially well demonstrated by plunging one hand into very cold water, in which case the temperature of the skin of the other hand is found to be diminished (*Brown-Séquard et Tholozan*). Slight cooling of one arm also causes a distinct diminution in the volume of the other, as may be shown plethysmographically (*Amitin, Lommel*). Similarly cold applied locally, by diminishing the blood content of the superficial portion of the body, especially in the skin and muscles, may cause a very pronounced alteration in the distribution of the blood, so that the abdominal organs receive a greatly increased blood supply (*O. Müller*).

This constriction of the cutaneous vessels resulting from the stimulus of cold protects the organism in a double fashion. First, a smaller portion of the total quantity of the blood is exposed to cooling in the skin, and consequently the blood returns to the heart at a less diminished temperature; and, secondly, more blood is diverted to the internal organs, in which its temperature is raised. As a result of this alteration in the distribution of the blood, the loss of heat caused by a lowered external temperature is limited, and the blood temperature remains constant so long as this physical heat regulation is sufficient to accomplish this end. When, however, it alone is no longer sufficient, as, for example, when one remains for a considerable time in a cold bath, a second regulatory mechanism is called reflexly into play,—the chemical heat regulation (*Rubner*).

In the latter case the organism protects itself by increased combustion, as shown by the fact that, when this chemical regulatory mechanism is called into play, the carbon dioxide output rises with the greatest regularity as the external temperature is gradually decreased (*Wolpert*). This reflexly augmented production of heat occurs chiefly in the muscles, and at the start without the occurrence of any visible movements, the increase in the production of heat being unaccompanied by any performance of mechanical muscular work. Besides the muscles, the great glands of the body also play a rôle in the production of heat, so that the reflexes resulting from external cold affect the functions of practically all the organs of the body.

Pharmacologically it is of some significance that the subjective feeling of cold and the protective processes which are excited by

stimulation of temperature nerves are dependent on the character and extent of the blood flow through the skin, for, if the cooling off of the skin is prevented by paralyzing the cutaneous vessels,—*e.g.*, by alcohol,—so that these, in spite of the low temperature, continue to receive large amounts of blood, the internal temperature of the body falls, but the individual does not feel cold because the temperature of the skin has not been lowered. Under these conditions, however, the stimulus, which causes the normal voluntary and involuntary protective reactions, which originate in the skin, is lacking, and, as a consequence, the body continues to lose more and more heat. This is the explanation of the danger of freezing to death which is caused by all narcotic poisons which paralyze the vessels of the skin, a danger which is especially great in alcoholic intoxication.

Like the regulation of the body temperature against cooling, the protection against overheating is also controlled by the nervous system, the cutaneous vessels being dilated, the secretion of sweat excited, and the respiration accelerated, so that more heat is given off through the skin and the lungs, all these effects being brought about by the activity of various nervous centres. The dilatation of the cutaneous vessels causes a larger quantity of blood to be exposed to the external cold, and the evaporation of the sweat from the surface of the skin absorbs a large amount of heat which is thus removed from the body. On the other hand, animals which are not able to sweat and which possess a thick hairy coat get rid of their superfluous heat chiefly by rapid breathing and the evaporation of water which results therefrom.

The dog, for example, is able to augment the heat loss from the skin only very slightly, and consequently he accomplishes his heat regulation by means of very rapid breathing, blowing the air over the widely protruded tongue, whose broad surface is kept constantly moistened with saliva and mucus and offers an exceptional opportunity for the evaporation of water. If dogs be forced to work and this very important regulatory mechanism be interfered with by previous tracheotomy, death ensues as a result of overheating (*Zuntz*).

In man, besides dilatation of the cutaneous vessels, the secretion of sweat is the most efficient means of removing large quantities of heat from the body, for the evaporation of 1 c.c. of water requires as much as 0.54 calorie, and consequently the excess of heat may be lost simply by the aid of the physical heat regulation, even during the performance of large amounts of mechanical work, as in marching (*Zuntz*), and, therefore, there is no need of a chemically regulated limitation of the production of heat to protect the organism from overheating.

Such regulation against overheating can also be directly called into play by a very slight increase in the temperature of the blood, for, without altering the temperature of the blood in the rest of the body, all the signs of the physical regulation against overheating may be

caused to appear by simply warming the blood in the carotid on its way to the brain, this alone being sufficient to cause dilatation of the cutaneous vessels, increased secretion of sweat, and heat dyspnœa (*Kahn*).

It is thus apparent that the heat-regulating centres can be stimulated to their reaction against a low external temperature not only reflexly but also by a diminution, even though a minimal one, of the temperature of the blood (*Stern, Strasser*), while in their reaction against overheating they are influenced both by the temperature of the blood and also reflexly from the skin, for such signs of compensatory regulation as sweating can appear under the influence of heat stimuli even before any augmentation of the temperature of the body has occurred (*Stern, Strasser, Filehne*). While this is true, still under all conditions it is the central nervous system which keeps the body temperature constant.

From what has already been said, it is evident that the physiological regulation of heat is accomplished by a very complicated mechanism, in which the vasomotor and secretory centres are influenced by a higher centre or centres. The organs in which the loss of heat occurs are connected nervously through such heat-regulating centres with the organs—the muscles and the glands—in which the heat is produced. Up to the present, however, our knowledge of the details of this relationship between these various regulatory processes is very incomplete. Certain it is only that the temperature equilibrium is maintained by this mechanism in such fashion that the production and output of heat always keep pace with each other so long as the heat-regulatory mechanism in the central nervous system continues to function normally. Under all the changing conditions of external temperature, as also in spite of all variations in the combustive processes in the organism, the body temperature remains constant, because, with every change in the metabolism,—as, for example, when food is ingested or when muscular work is performed,—the output of heat simultaneously changes in a corresponding direction, and because, if this physical regulation does not suffice, the production of heat is also regulated so as to correspond to the changing demands occasioned by the loss of heat. In this fashion the equilibrium of the heat economy of the body can be maintained, even in spite of very great variations in the amount of heat produced or lost. The maintenance of the normal body temperature depends simply on any alteration of one factor being compensated by a regulatory alteration of the other, so that the momentary heat loss may always equal the momentary heat production, the amount of heat in the body being thus kept constant.

These relationships may be expressed by a diagram (see Fig. 55), in which the changing values of heat production and output are shown

as ordinates. Under normal conditions they coincide with each other, and there is no interval between them so long as the body temperature remains normal.

The curve below represents the body temperature under different conditions. It remains normal if under normal conditions the production and output of heat are equal, also when both are equally increased, as, for example, during muscular work. In long-continued hunger the body temperature falls as a result of the diminution of the production of heat. In fever it rises, because of the lagging behind of the heat output and because of the increase in the heat production which then follows. In the crisis it falls, because the heat production lags behind the heat output.

Fig. 55.

Such a coördinated coöperation between heat production and heat loss could be obtained only by a centrally connected control of both processes, for the controlling heat centres must necessarily be able both to influence the organs through which heat is lost and to control the metabolism in the tissues.

The reaction of these heat centres to cooling may be interpreted as consisting in an augmented state of excitation of the regulating centres. Even under normal conditions stimuli are carried through the sensory centres of the skin to the centres for the constriction of the cutaneous vessels, and, if the temperature of the skin falls, this reflex stimulation becomes stronger, and consequently the heat output is diminished. The chemical heat regulation,—that is, the augmentation of the processes by which heat is produced,—which is excited by cooling of the body, also depends upon an augmentation of the nervous impulses which accelerate the chemical processes in the muscles, which can even be so augmented as to cause visible muscular movements, such as shivering when one is chilled. That this conservation and production of heat is due to an augmented excitation of the centres is indicated, above all, by the fact that the same effects, diminution of the output and augmentation of the production of heat, may also be produced by direct mechanical or electrical stimu-

lation of certain regions of the brain (*Aronsohn u. Sachs, Richet, Ott*). In the rabbit, dog, and horse such a point lies in the head of the corpus striatum.

The reaction of the organism against overheating can, on the other hand, be assumed to be due to a depression of the excitability in the same centres, these centres, under the influence of overheated blood, moderating the impulses which they send to the vasomotor centres. In accordance with this is the observation of *Kahn* that overheating of the carotid blood acts as a sedative on other centres also, the animals being, as it were, narcotized. These assumptions are in no way inconsistent with the fact that, associated with this sedative action on these regulatory controlling centres, there is an augmented activity of the subsidiary centres, which causes secretion of sweat, heat dyspnœa, etc., for often enough in physiology one meets with examples of such opposing actions on controlling and subsidiary centres.

It will be shown later that the actions of pyrogenous poisons and of antipyretics are quite consistent with this assumption that conservation of heat is due to a stimulation of the heat-regulating centres, and that increased output of heat is due to sedative action on them.

Although we speak of heat-regulating centres, it is by no means implied that these have been anatomically located, for anatomically we know of no heat centre. The structures affected by the heat puncture may be centres or —and quite as probably—simply nervous tracts which are connected with various scattered centres. However, we are forced to assume in a physiological sense a heat-regulating centre, meaning by this term a controlling central mechanism, which secures a coördinated coöperation of vasomotor and sweat centres, and which also furnishes the necessary nervous impulses to control the metabolism, so that the equilibrium of the temperature may be maintained. These centres certainly do not lie lower than the midbrain, for, after destruction of this or after high division of the cord, warm-blooded animals behave like cold-blooded animals, their body temperature becoming dependent on the temperature of the environment.

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FEVER

In infectious diseases pyrogenous substances, by their action on the heat-regulating centres, cause a rise in the body temperature (*Krehl*), for bacterial toxins cause a toxicogenic decomposition of proteids, and the peculiar products of this pathological decomposition of protoplasm or the bacterial toxins themselves disturb the normal processes of heat regulation.

Various investigations of the production and conservation of heat in febrile men and animals (*Krehl u. Matthes*) have shown that, as a rule, while the heat production is distinctly augmented, this augmentation is not very great, amounting to only about 20–30 per cent. increase above the normal value (*Krehl*). Inasmuch as in the organism, so long as the heat regulation is functioning normally, the production of heat may be increased as much as 60 per cent. by the free ingestion of food, and by muscular work even more, without the temperature rising, it is evident that a 30 per cent. increase in heat production cannot by itself be the cause of the augmentation of the temperature, and consequently in fever there must also be some other disturbance of the temperature regulation. This is in fact the case, for, while normally an increase in heat production is readily compensated for by increased heat output, this latter is either absolutely diminished in fever or is less increased than is the heat production.

Calorimetric determination of the total heat output of febrile animals (*Krehl u. Matthes*) shows that this is diminished during the period in which the fever is rising, and in man the coldness and pallor of the skin during the chill, by themselves, show that the cutaneous vessels are contracted. This has been definitely proven by *Maragliano's* plethysmographic studies and by *Geigel's* and *Kraus's* thermo-electric investigations. Furthermore, *C. Rosenthal's* partial calometric observations have demonstrated the diminution of the heat loss by conduction and radiation.

It is thus evident that in fever the temperature rises as a result of limitation of the heat output while at the same time the heat production is, as a rule, augmented. In fever the organism behaves as if it were necessary to conserve its heat, combusting more material than ordinarily and parting with as little of its heat as is possible.

One might be tempted to conclude that in fever the heat centres had entirely lost control of the peripheral mechanism by which heat is lost and produced, and that consequently they are no longer able to maintain a balance between these two functions. This, however, is not at all the case, for, as shown by *Liebermeister* and *Stern* in man, and by numerous others (*Colasanti, Finkler, Lilienfeld,* etc.) in febrile animals, the febrile organism reacts to cooling influences by augmentation of heat production and to artificial overheating by increasing its heat output. However, the heat regulation is no longer so efficient or complete as in normal conditions, and consequently the

febrile temperature is more readily altered by external influences than is the normal temperature.

From the above it is evident that in fever the body has by no means lost its power of heat regulation, but, as production and loss of heat are no longer so controlled that the normal temperature is maintained and as, on the contrary, the febrile organism regulates these processes in such a fashion that it maintains its abnormal temperature, we are compelled to conclude that in fever the heat-regulating centres function in an abnormal fashion. As long ago as 1875, such observations led *Liebermeister* to formulate the hypothesis that in fever the heat regulation is " set " for a higher temperature. As a matter of fact, at the height of any fever a regulatory augmentation of the heat output occurs, for otherwise the temperature of the body would rise constantly higher and higher because of the constantly increasing augmentation of heat production. However, so long as the pathological condition of the heat centres persists, the heat loss is augmented only enough to maintain the temperature at a febrile height, but not enough to bring it back to normal.

To-day it is possible to form a more precise conception of the manner in which in fever the heat mechanism is " set " for an abnormal temperature, and of the manner in which this is corrected by antipyretics (*Filehne*). An analogy between infectious fever and puncture hyperthermia has been of much assistance here, for it has been found that heat regulation in both of these types of fever is essentially similar. In the fever resulting from the mechanical irritation of the corpus striatum there is an augmentation of the heat production (*Schultze*), while during the period of rising temperature the heat output is absolutely diminished or at least relatively insufficient (*Gottlieb, Richter, Schultze*), just as in infectious fever. In it, too, the power of regulating the temperature is retained and comes into action when the external temperature changes (*Schultze*). At the height of the fever thus produced, the heat output is augmented, just as in infectious fever, but only enough to enable the organism to maintain its febrile temperature. It is thus seen that there is a wide-reaching analogy between puncture hyperthermia and infectious fever.

Although the pathological condition of the heat-regulating mechanism is essentially the same in both cases, it is due to different causes, for the disturbance produced by the heat puncture is a direct one, and consequently less complicated, while the alteration of this function in fever is due to the action of toxins and is accompanied by all the other effects of the infection.

This accounts for certain differences in the two types of the fever. For example, in puncture hyperthermia primarily non-nitrogenous material is combusted, apparently chiefly the glycogen of the liver and muscles (*Hirsch u. Rolly*), while in infectious fever it is principally nitrogenous material rendered available by the pathological decomposition of proteid which furnishes the material for the increased combustion. When the reserve substances have

been completely consumed, heat puncture causes no fever (*Hirsch*), a fact which has been interpreted by some as indicating an essential difference between it and true fever. However, the occurrence and extent of the increased combustion both depend upon the presence of readily available material, which in true fever is always available in the form of nitrogenous material resulting from the decomposition of protoplasm, although ordinarily such material is tenaciously protected in fasting and emaciated individuals.

However, this difference between puncture hyperthermia and infectious fever is not a fundamental one, for in fasting animals it has been found that no rise of temperature results from the injection of albumoses and other pyrogenous substances which ordinarily cause a septic fever (*Krehl u. Matthes*).

Consequently, everything speaks for the assumption that the fever of infection and that following heat puncture are due to a basically similar action upon the heat-regulating centres. This parallelism between the two types is of importance for our understanding of the pathology of fever as well as for our understanding of the action of the antipyretics, for the augmentation of the temperature following the heat puncture is, without any doubt, to be attributed to the trauma's causing a stimulation of the heat-regulating centres. The main evidence that this is so is found in the fact that the temperature may be augmented by electric stimulation by means of electrodes fixed at the proper place in the corpus striatum. We may then conclude that the alteration of the heat regulation resulting from heat puncture is due to stimulation or irritation of these centres, and are justified in assuming the same for fever. When we say then that the heat-regulating mechanism is " set " for a higher temperature, we mean that the heat-regulating centres are in a condition of pathologically augmented excitability.

While in puncture hyperthermia this excitation is produced by mechanical or electrical irritation, in infectious fever we are dealing with an irritation produced by toxic substances, parallels for which may be found in the various other symptoms of irritation observed in fever. In both cases the excitability of the heat-regulating centres is so altered that they react so as to conserve heat to stimuli which are weaker than those ordinarily adequate,—*i.e.*, this reaction occurs without any actual cooling of the body. However, in a normal reaction to cooling, the excitation of the centres lasts only as long as is necessary to maintain the body temperature, but when their excitability is pathologically increased the augmentation of metabolism and the limitation of heat output persist until that degree of temperature is attained at which the sedative action of the increased temperature of the blood counterbalances this. When, then, in the course of the sickness the augmented excitability passes off again, the centres react once more in a normal fashion to the overheated blood, so that the heat output is again augmented until the normal temperature is regained.

There is no contradiction between this conception of fever, as due to a persistent abnormal stimulation of the heat-regulating mechanism, and the well-known fact that, generally speaking, the body temperature in fever is more

unstable than in health, for a similar behavior of irritated organs is often enough observed (*Loewi*). The slighter resistance manifested by the febrile organism to frigorific influences may be conceived of as the expression of the fact that the irritated centres are more readily fatigued.

From the foregoing, the action of pyrogenous substances must be attributed to a stimulation or an augmentation of the excitability of the heat-regulating mechanism. Fever results from the invasion of the pathogenic organisms, and persists as long as the body, with the assistance of its defensive weapons (antitoxins, bacteriolysins, etc.), is able to continue the battle; but when it succumbs, collapse develops and the temperature falls. It consequently appears probable that certain substances, which are formed as a result of the death of the pathogenic organisms, act as pyrogenic poisons, which stimulate the heat-regulating centres and in larger amounts paralyze them. Heterogeneous proteid also, when it disintegrates in the body, causes a rise of temperature, which, under the peculiar conditions of hypersusceptibility to heterogeneous proteid, expresses itself as an anaphylactic fever. Moreover, the decomposition products of homologous cells—for example, the albumoses—also act as pyrogenetic agents (*Krehl u. Matthes*). Apparently a large number of substances, particularly when administered intravenously and in the presence of hypersusceptibility, cause a septic fever by causing decomposition of cells or of proteid (*Krehl*). While the mechanism by which this is accomplished has not been cleared up, it is not improbable that a stimulation or augmentation of the excitability of the sympathetic nervous system, to which consequently the heat-regulating centres also probably belong, plays a causative rôle in the production of such fever.

In favor of this view is the fact that tetrahydronaphthylamine (see p. 159) has a marked power of raising the temperature (*R. Stern*), and that, moreover, many drugs, like caffeine, cocaine, and atropine, which, generally speaking, stimulate many of the nervous centres, cause an increase of the temperature, even quite independently of the secondary effects of any convulsions which they may cause. These are all drugs which cause other symptoms of stimulation of the sympathetic or depression of the antagonistic autonomic system, such as pulse acceleration, mydriasis, psychic stimulation, etc.

That, on the other hand, other drugs which also stimulate various centres, such as the convulsant poisons like santonin, picrotoxin, aniline, phenol, etc., do not raise the temperature, but in fact under certain conditions markedly depress it (see p. 473), does not speak against such a conception, but rather confirms our interpretation, for these drugs do not stimulate the sympathetic nerves, but, on the contrary, stimulate the antagonistic autonomic centres, causing slowing of the pulse, miosis, psychic depression, etc. Finally, moreover, the typical sympathetic poison, epinephrin, can under certain conditions cause a marked augmentation of the temperature (*Eppinger, Falta u. Rudinger*), and it appears probable that this epinephrin

fever is due to a central or peripheral stimulation of the sympathetic system. In the fasting animal and in narcosis, epinephrin causes no rise in temperature, and calcium salts, which depress the excitability of all organs which are susceptible to epinephrin, also prevent or lower fever thus caused (*Freund*).

According to this last-mentioned author, sodium-chloride fever is of a similar type. This was first observed in infants after the administration of large quantities of common salt (*Finkelstein, Schloss*), but may also be induced in adults in about 50 per cent. of the cases (*Bingel*), and even more readily in animals. It would appear that this sodium-chloride fever is also due to stimulation of the sympathetic nervous system.*

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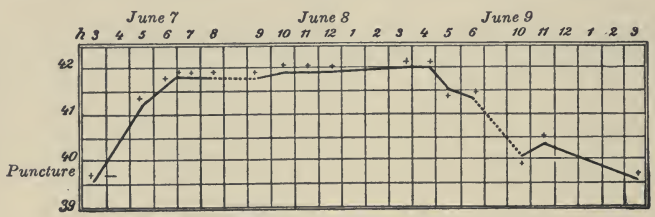
ACTION OF ANTIPYRETICS IN FEVER

The conception of fever as caused by over-excitability of the heat-regulating centres is useful in explaining the antipyretic effects of certain drugs, in considering which it is advantageous to use as a starting-point the simpler fever that follows puncture (*Gottlieb*).

If the fever following heat puncture in the rabbit be allowed to run its course without interference, the curve exhibits the characteristics of continuous fever.

* [As a result of recent investigations of the effects of the intravenous injection of normal saline solutions made up with freshly distilled water as contrasted with those made up with distilled water which had stood some time, considerable doubt has been thrown on the earlier experiments which appeared to demonstrate the possibility of a sodium chloride fever.—Tr.]

After the preliminary fall of the temperature due to the shock of the operation, the fever within a few hours rises markedly, and maintains itself without marked variation for 12–24 hours at about 41–42° C. and then very gradually returns to normal.



FIGS. 56.—Normal course of puncture hyperthermia.

In other particulars such rabbits manifest no other disturbances of function, and continue to eat and appear quite normal. A dose of antipyrine causes a sharp depression in this very regular course of the temperature curve.

Without producing any other noticeable effects, 0.5 gm. of antipyrine administered to such a rabbit brings the temperature back to normal, but after about two hours the temperature commences to rise again, and after about 6–8 hours, when the effects of the drug have passed off, regains its original height.

The more the effects of the puncture in causing stimulation of the heat centres have passed off before the antipyretic is administered, the greater is the effect of the drug in bringing about a changed "setting" of the centre,—*i.e.*, in lessening its excitability. Consequently, at the summit of the temperature curve or in the descend-

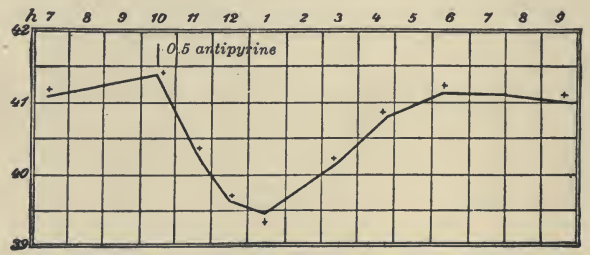


FIG. 57.—Effect of antipyrine on puncture hyperthermia.

ing portion, antipyrine acts more strongly than during the period in which the temperature is rising rapidly. The other drugs belonging to the same pharmacological group act here just like antipyrine.

It is of decisive importance for the interpretation of these phenomena that, on the one hand, the puncture hyperpyrexia is conceived of as due to stimulation of the heat centres and that, on the other hand, all typical antipyretics are narcotic in their nature. Consequently it may be concluded that the antipyretics owe their

action to their power of acting as sedatives to the pathologically stimulated heat centres. If any further proof of the correctness of this conception were necessary, this is furnished by the observation that other drugs which without any doubt act as central depressants—for example, small doses of morphine—lower the temperature of puncture hyperthermia, even in the rabbit, which is, generally speaking, very insusceptible to this drug.

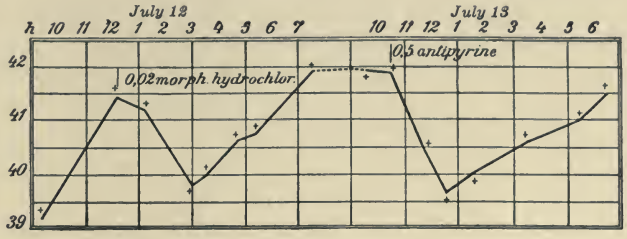


Fig. 58.—Effects of morphine and of antipyrine on puncture hyperthermia.

The antipyretics consequently are narcotics of the heat-regulating centres of the brain. Their basic narcotic character, however, does not show itself solely in their sedative action on the heat-regulating mechanism, for their mild depressing action is just as clearly manifested in the sensory portion of the cerebral cortex. Consequently the more powerful antipyretics cause a more or less pronounced condition of sleepiness and of diminished sensibility in laboratory experiments. Above all, however, clinical experience has taught us that all the antipyretics are at the same time analgesics and sedatives,—*i.e.*, mild narcotics for the sensory cerebral tracts.

From what has already been stated, it is clear that the combination of antipyretic and sedative action in all the drugs of this group is not merely a coincidence, for both of these properties are the expression of a mild narcotic action on the cerebrum, the elective seats for this action being assumed to lie, on the one hand, in the cerebral cortical centres for the perception of pain (just as is the case with morphine) and, on the other hand, in the heat-regulating centres which are over-stimulated in fever. For these reasons *Schmiedeberg* has very appropriately given to the drugs of the antipyrine group the name of *fever narcotics*. This name, moreover, correctly characterizes this group of drugs, inasmuch as modern medicine employs them in fever but seldom as a means of combating the hyperpyrexia as such, but rather in the hope that the patient will be benefited by their sedative action on all those symptoms of fever which are due to over-excitability of the centres.

It is quite in accord with the conception of the antipyretics as sedatives of the heat centres that those doses which are effective in fever do not influence the temperature in health, although larger doses

do produce a lowering of the temperature even in health. The explanation of the stronger effect on the excitable heat centres of fever is found in the general experience that nervous centres, when in a condition of persistent over-excitability, are, as a rule, more readily fatigued, and consequently more susceptible to the action of narcotics. The same thing is observed to a very striking extent in the physiological effects of strychnine, in which over-excitability and ready exhaustibility of the reflex centres go hand in hand.

The therapeutic action of the antipyretics as described thus far should, however, be clearly differentiated from a true paralysis of the heat-regulating mechanism, for, after effective doses of antipyrine, animals still react very decidedly to changes in the external temperature, although not so promptly as untreated controls. The power of regulating the body temperature is lost only after very much larger doses, this being simply one of the results of the general collapse which is caused by larger doses.

Collapse.—Numerous poisons and drugs cause collapse with a marked fall of blood-pressure, both effects being the result of a commencing paralysis of the vital centres. Particularly with the narcotic drugs and poisons the therapeutically effective doses lie relatively near to those which cause collapse. Like the narcotics, substances of the carbolic acid group, the salicylates, and members of the antipyrine group, all of which are closely related pharmacologically, produce such conditions of paralysis relatively easily. In such collapse the temperature of the body falls, but this lowering of the temperature by depressing the various nervous centres differs from the elective antipyretic action in its entirely different symptomatology and in the different manner in which it is produced. In collapse, as the temperature falls, the pulse becomes small and weak, the extremities grow cold, and all those symptoms develop which are spoken of as cardiac weakness. As a result of depression of the vasomotor centres, the rapidity of the blood circulation is so diminished that only small amounts of heat are lost through the skin, and at the same time the heat production is diminished as a result of a centrally induced diminution of heat production (*Krehl u. Matthes*).

There is no doubt that a number of drugs formerly much used in fever—for example, veratrum and aconite—produce a narcotic effect on the over-excited heat-regulating centres similar to that produced by our modern antipyretics. However, they differ from these latter in that their actions are not so electively confined to the heat-regulating mechanism, and, as a consequence, with them antipyretic effects result only from such doses as lie very close to the dangerous ones which may cause collapse. As a consequence, these drugs have been abandoned, and correctly so (see pp. 109, 426).

Pyrogenic poisons also very readily cause collapse, causing in small doses an augmentation and in larger doses a fall of the temperature, which is accompanied by a diminution of both the production and the output of heat (*Krehl u. Matthes*). Fever may, therefore, be considered as a symptom of stimulation produced by small amounts of toxins, and collapse as a symptom of the paralysis caused by larger amounts of these substances.

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COLD BATHS

Following the discussion of the more pronounced alterations of febrile temperature produced by antipyretic drugs, the entirely analogous action of cold baths should be briefly considered.

The temperature of a healthy individual does not fall at all as a result of such moderate abstraction of heat as results from ordinary hydrotherapeutic measures. In fact, at the start the internal temperature rises for a short time (*Liebermeister*), because, by the contraction of the cutaneous vessels, the blood is driven out from the region in which normally it is cooled, and it is only during the so-called primary after-effect that the temperature may fall slightly, if after the bath the cutaneous vessels relax so that larger than normal amounts of blood may flow through the cooled-off skin.* Under normal conditions, the physical regulation by constriction of the cutaneous vessels and the chemical regulation by increased combustion of non-nitrogenous substances are sufficient to keep the temperature of the body constant within very narrow limits. However, the power of heat regulation, even in health, has a limit, and the temperature of the body sinks if the temperature of the bath is extremely low and its duration very long, this occurring more readily in small and poorly nourished than in large and fat individuals.

In the febrile patient, on the other hand, the temperature is much more markedly lowered even by very moderate cooling, and often remains somewhat depressed for hours. It is thus evident that in fever the heat regulation exhibits the same instability in its reaction to measures by which heat may be abstracted as to medicinal antipyretics. Just as with antipyrine, the heat production in a febrile individual is augmented to a slighter degree by abstraction of heat than is the case in health. Particularly in the period of after-action, in which the diminution of the temperature becomes more pronounced, the chemical heat regulation of the febrile patient more readily proves itself insufficient. This effect is augmented further by the fact that in many febrile conditions the vasomotor centres tire particularly easily, so that, after being contracted during the bath, in the after-period the tone of the cutaneous vessels is markedly diminished and for a considerable period (*Krehl*).*

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* [Such reaction is favored by continuous friction of the body during the bath. That this is so may be readily demonstrated by comparing the after-effects on the temperature produced by baths given with such friction, with those following similar baths given without it.—Tr.]

DIRECT ACTIONS OF THE ANTIPYRETICS ON HEAT PRODUCTION AND HEAT LOSS

Thus far we have spoken as if only the central heat-regulating mechanism were affected by the antipyretics. On closer examination, however, the conditions are found to be more complicated. This is dependent on the fact that the action of the antipyretics is not limited to the heat-regulating centres alone, but that certain of them also affect the heat economy of the body by influencing the output or formation of heat independently of the central regulating mechanism. From this point of view we may differentiate between **two groups of antipyretics:**

Those of the **antipyrine group,** which cause cutaneous vasodilatation and directly increase the heat loss; and

Quinine, which lessens the production of heat by a direct action on the various metabolic processes in the tissues. The phenomena of defervescence, as it actually occurs, are in part due to these direct actions on the functions of heat output and heat production.

ACTION OF THE ANTIPYRINE GROUP ON THE HEAT OUTPUT

If antipyrine acted only on the central heat regulation, and changed the over-excitability of the centres to a normal condition without directly and independently interfering with the heat economy of the body, it should be expected that under its influence the body would get rid of its superfluous heat in the same fashion as in spontaneous defervescence. In spontaneous reduction of the temperature the production of heat is reduced to the normal or even below this (*Krehl u. Matthes*), but, above all, the output of heat is so influenced that critical defervescence in infectious diseases is followed by marked dilatation of the cutaneous vessels and profuse sweating. The same phenomena then should occur if a dose of antipyrine has brought about a normal condition of the heat centres, and, as a matter of fact, in defervescence produced by antipyrine the behavior of the organism corresponds in many cases to this type (*Stühlinger*).

However, it does not always do so, for antipyrine possesses the power of dilating the cutaneous vessels independently of the heat-regulating mechanism and to an even greater degree, and even in health this effect may be produced by doses which do not lower the temperature, and which consequently are incapable of affecting the tone of the more resistant heat-regulating centres of the healthy individual. As a result of this cutaneous vasodilatation, antipyrine increases the heat loss in health as well as in fever. That the temperature does not fall is due to a compensatory augmentation of the heat production, which opposes the alteration of the temperature as long as the heat-regulatory mechanism is capable of functioning normally (*Gottlieb*). This compensatory augmentation of combustion is the explanation for the often considerably increased excretion of nitrogen which antipyrine and related substances cause in healthy men in whom the heat regulation acts promptly.

While in the healthy man this prompt regulation of temperature is overcome only by much larger doses than are used therapeutically, in fever such

doses of antipyrine do weaken this regulatory function, and, as a consequence, there is no longer so great an increase in the heat production as there is in the heat loss, and consequently the body temperature falls.

This attempt of the organism to combat the augmented heat loss caused by antipyrine is also manifested in many cases of fever when the temperature falls, causing, just as in the healthy individual, a compensatory augmentation of heat production, which is not to be disregarded, for it necessarily results in an increased consumption of tissues. This regulation against heat loss is, it is true, often but slight in febrile patients (*Riethus*), and consequently the diminution of heat production which results from the defervescence more than counterbalances it. The reauction of febrile temperature by antipyrine may be schematically represented in the accompanying diagram.

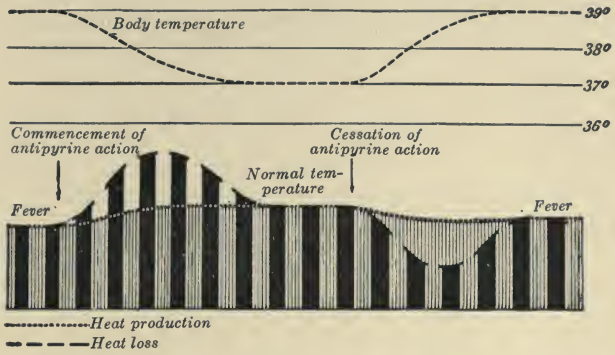

Fig. 59.—Antipyretic effect of antipyrine. Augmentation of heat loss with slight compensatory increase in heat production.

Antipyrine and related substances consequently reduce the temperature principally by augmenting the heat loss, as is indicated by the simple direct observation of the hot and reddened skin and as has been demonstrated thermoelectrically by *Geigel* and plethysmographically by *Maragliano*. This cutaneous vasodilatation is not simply one symptom of a generally diminished vascular tone, but is the result of an antagonistic behavior of the vessels of the skin and those of the internal organs. As this does not lower the general blood-pressure, and may in fact increase it, large quantities of blood are caused to flow through the dilated vessels on the surface of the body, where the fever-heated blood has an opportunity to give off its superfluous heat, this bringing about an increase in the heat output, which has been demonstrated both in animals (*Gottlieb u. Richter*) and, by partial calorimetry, in man (*Rosenthal*).

It must again be emphasized that the above-described augmentation of the heat loss is not the true cause of the antipyretic action of antipyrine, for the augmentation of heat loss, which, according to calorimetric determinations, seldom exceeds the normal by more than 20–30 per cent., is much too slight to overcome a normally functioning heat regulation. Consequently, in a healthy man the temperature is not altered, in spite of such increased heat output, but, owing to the greater ease with which the over-stimulated and at the same time

readily fatigued centres of fever may be influenced, even smaller doses are sufficient to produce a sedative effect on the heat-regulating centres. This sedative action on the central heat regulation is to be considered as the real cause of the antipyresis, while the directly produced augmentation of the heat loss is to be regarded simply as a simultaneous clearing of the paths by which the superfluous heat is eliminated.

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ACTION OF QUININE ON HEAT PRODUCTION

The temperature in healthy men and animals is either not diminished at all or only very slightly, even by doses of quinine much larger than those which are effective in fever (*Stühlinger*). In fact, after smaller doses the temperature not infrequently rises (*Jansen, Friedmann*), a paradoxical effect which may be produced by other antipyretics and for which no satisfactory explanation can be given.

If the action of quinine is studied on animals in the calorimeter, it may be demonstrated that the fall in the body temperature is chiefly the result of a limitation of the heat production (*Gottlieb*) while at the same time the heat loss is augmented to a slight degree. The reduction of fever caused by quinine, consequently, may be diagrammatically represented as follows:

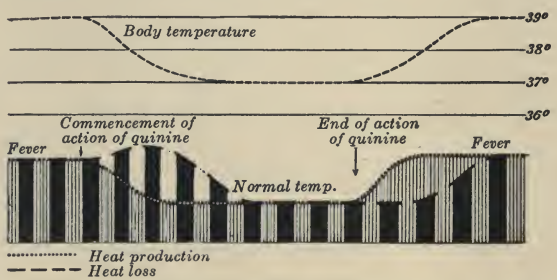

FIG. 60.—Antipyretic effect of quinine. Heat production diminished and heat loss slightly increased.

The limitation of heat production by quinine is a primary or direct action, occurring even after separation of the body from the heat-regulating centres by section of the cord. *Krehl* and *Matthes* investigated the behavior of the temperature of rabbits thus prepared at the temperature of 27° C., and found that quinine * under such conditions caused a marked diminution in the amount of heat formed, while antipyrine produced no effect whatever. This

* See, in this connection, *Naunyn u. Quincke* and *Binz.*

indicates that antipyrine acts upon the heat economy only through the central nervous system, while quinine, even after the elimination of all central nervous influences, diminishes the metabolism of the tissues. In agreement with this, quinine also lessens the production of heat in surviving organs, as shown by *Binz's* observations that after section of the cervical cord no post-mortem rise of temperature, or only a very slight one, occurs in rabbits which have taken quinine, even though heat loss be prevented, although in the controls there was a very marked post-mortem rise.

In a similar fashion, the addition of small amounts of quinine to the blood inhibits the usual formation of acid (*Binz*), as also the synthesis of hippuric acid in the surviving kidney (*A. Hoffmann*), and probably other syntheses and decompositions (*Laqueur*) in the tissues are inhibited by quinine, perhaps by inhibition of the intracellular ferments by quinine (see Metabolism, p. 403), so that the heat production in the tissues is directly inhibited.

However, it cannot be concluded that the antipyretic action of quinine is entirely the result of this action on the metabolism, for, even though the total result of the heat-producing processes is diminished by quinine, this diminution is always so slight that it could be readily compensated for by an appropriate increase of the heat loss if the heat-regulating mechanism were functioning normally. The reduction of fever produced by quinine must, consequently, have still another cause, which, in those cases in which its action is not a specific one as it is in malaria, is found in an action analogous to that of antipyrine,—*i.e.*, in a sedative action on the heat-regulating centres. However, this central action of quinine is less powerful than that of the antipyrine group, a fact which is demonstrated by the relatively weak action of quinine in puncture hyperthermia. In this condition the temperature is lowered by quinine only in the descending portion of the temperature curve, when the hyperthermia already of its own accord shows a tendency to abate. It is thus evident that quinine acts much less energetically on the function of heat regulation than does antipyrine (*Gottlieb*), and, consequently, it too in non-toxic doses hardly lowers the temperature in health, and exerts an antipyretic effect only when the heat-regulating function has become abnormally susceptible,—*i.e.*, only in fever.

The reduction of temperature induced by quinine results, just as in normal defervescence, from augmentation of the heat output and diminution of its production. Quinine consequently, as a result of its slight action on the heat-regulating centres, also aids spontaneous defervescence, which effect is aided by the direct diminution of heat production resulting from its action on the metabolism, and, as quinine primarily limits proteid metabolism, it aids the organism in conserving its most valuable material.

However, by no means all fevers may be successfully combated with moderate doses of quinine. The more marked effect of quinine in certain infectious fevers,—*i.e.*, in typhoid (*Erb*)*—is perhaps due to a direct action on the cause of the fever, resembling its specific action on the malarial organisms (see Etiotropic Agents, p. 527).

* [This is certainly doubtful.—Tr.]

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THE SALICYLATES

Salicylic acid apparently occupies a position between quinine and the antipyrine group. In common with quinine, it appears to have the property of acting directly on the cause of the fever in acute articular rheumatism and in many other infections, and, like it, salicylic acid too has comparatively little effect on puncture hyperthermia. In these particulars it stands close to quinine and in a certain opposition to the antipyretics which act purely symptomatically.

On the other hand, salicylic acid stands closer to antipyrine in respect to the manner in which it lowers the temperature in fever. Particularly in those conditions in which it acts only on the fever and not on the cause of the disease, it not only does not lessen proteid metabolism but, on the contrary, very markedly increases it (*Kumagawa, Virchow, Salome,* etc.). The reduction of febrile temperature by salicylic acid is due, as is the case with the antipyrine group, to an augmentation of heat loss, particularly as a result of sweating, and the later rise of the temperature may often actually be accompanied by a chill. However, the behavior of the heat economy of the body under the influence of the salicylates has not been sufficiently studied to permit of a closer knowledge of its details.

Acetyl-salicylic acid, introduced by *Dreser* under the name of aspirin, appears to stand much nearer to the antipyrine group. It lowers the temperature caused by the heat puncture much more strongly, and is consequently more effective as a purely symptomatic antipyretic than is salicylate of soda (*Bondi u. Katz*). Although aspirin is excreted only after being decomposed, it may be absorbed without undergoing decomposition, for this occurs but slowly in the intestine. Consequently, before it is decomposed with the formation of salicylic acid by the ferments of the tissues, it may be differently distributed and produce other actions than its mother substance.

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OTHER ANTIPYRETIC AGENTS

Many other substances also possess the power of depressing the temperature. In general this power is a characteristic of many benzol derivatives,—for example, of carbolic acid, which may serve as a prototype of the aromatic antiseptics (*Harnack*). While the antipyretic action of phenol may not be utilized therapeutically because of its other toxic actions, and while other substances chemically closely resembling carbolic acid (hydroquinine, etc.) are too poisonous and often produce collapse, various aniline and paramidophenol derivatives, formed by introduction of acids into their molecules, are comparatively non-toxic antipyretics.

As a part of their general narcotic action, moreover, many *narcotics of the alcohol group,* in particular *alcohol* itself, exert a sedative action on the heat-regulating centres, and in large doses paralyze them, so that collapse with a marked fall of body temperature develops.

On the other hand, it has long been known that the powerful central stimulant *camphor,* when given in large doses, lowers the temperature in fever (*Hoffmann*). *Harnack* and his collaborators have also found that other convulsants, particularly *picrotoxin* and *santonin,* may also lower the body temperature independently of any convulsions which they may cause. The same is true for *aniline,* which also possesses a convulsant action (*Schuchardt*). Moreover, the combination of santonin or picrotoxin with chloral, amylene hydrate, ether, or chloroform, etc., which of themselves possess but slight power to lower temperature, produces a tremendous fall in the temperature, which is much larger than is accounted for by the sum of the effects of each of these components. Evidently, while both of these groups of antithermic drugs act on the heat-regulating centres, their points of action are certainly different, as is evidenced by the different behavior of the temperature when cocaine is administered to animals in which the temperature has been lowered by some member of one or the other of these groups (*Harnack u. Schwedmann*).

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THERAPEUTIC EMPLOYMENT OF THE ANTIPYRETICS

Up to a few years ago physicians believed that it was necessary to give antipyretics in the presence of any marked febrile augmentation of the temperature. This routine endeavor to combat fever was due to theoretical conceptions which, ever since the middle of the last century, have led to the assumption that the anatomical alterations observed in the parenchymatous organs after severe infection were produced by long-continued high temperature. (In this connection see *Krehl.*) Hence the fear of fever. The introduction of the modern antipyretics, which permit the prompt reduction of temperature without producing harmful side effects, was a welcome aid

in this endeavor to combat fever, for by their use it was possible to cause even such a disease as typhoid to run its course without fever.

However, it was just this energetic employment of antipyresis which has taught us that by no means all the supposed dangers of fever are due to the augmentation of the temperature as such, and to-day, as a result of the experimental investigations of *Naunyn, Pflüger, Finkler, Unverricht,* and others, it is known that these pathological changes are not the results of the increased temperatures, but that they are a coördinate effect, which, like the alterations in the function of heat regulation, is dependent upon the intoxication produced by the specific infectious poisons.

The augmentation of the temperature is a reaction of the central nervous system to its invasion by these poisons, and is thus a symptom of which we cannot decide *a priori* whether it be harmful or useful to the organism. In more recent times the conviction has gained ground that fever as such is harmless, and we have been more and more inclined to the view—which, by the way, is hundreds of years old—that the rise of temperature represents a curative effort of nature,—*i.e.,* that it is a defensive reaction of the diseased organism, which is useful to it in its struggle with the cause of the disease and of the fever. In many particulars present investigations support this view, for augmentation of the body temperature by overheating (*Filehne, Walther, Rovighi*) or by heat puncture (*Loewy u. Richter*) appears to exert a favorable influence on the course of experimentally induced infections.

In what fashion such high temperatures produce their favorable effects is not entirely clear, but it is less probably due to a direct effect upon the growth and virulence of the bacteria than to the effect of the increased temperature in augmenting combustive processes and in producing a more active formation of the various protective substances (*Kast, Krehl, Rolly, Meltzer, Lüdke*). Thus, for example, it has been shown that, when the formation of antibodies had already become less active, the amount of these substances in the blood of infected rabbits increased again if their temperature was raised by heat puncture (*Aronsohn u. Citron*).

Consequently, it is not the augmentation of temperature as such which should be combated, but only certain accompanying phenomena. Among these it is certain that the accelerated action of the heart, the dyspnœa, and at least a portion of the augmentation of metabolic processes are to be considered as due to the abnormal temperature, and, in case of excessive hyperpyrexia, these may become distinctly dangerous to the patient. Consequently an excessive degree of an otherwise useful reaction must be combated by antipyretics. Moreover, various other symptoms present in infectious diseases—above all, the restlessness, headache, anorexia, etc., of the febrile patient—

are favorably influenced by the calming action of the antipyretics. Consequently, one uses the antipyretics more to secure their sedative effects than to lower the temperature, just as to-day one uses hydrotherapy in fever rather for its favorable effect on the sensorium and the circulation and respiration than for its power of lowering temperature. Consequently, it is the pharmacological property of the antipyretics of acting as "fever narcotics" which is the chief factor in their therapeutic value. In addition to this, we cannot deny that in infectious fevers they may exert other unknown actions which would account for their favorable influence on various symptoms.

Analgesic and Hypnotic Actions.—The narcotic mild "morphine-like" action on the algesic centres comes into play when they are used in the presence of neuralgic pains of different kinds. It is possible that the almost specific action of these drugs in neuralgias is in part due to an increased determination of the blood to the periphery of the body. In headache their power of relieving spasm of the cerebral arteries may play a rôle, for *Wiechowski* has found that a very large majority of the analgesics of the group dilate the cerebral vessels as well as the cutaneous ones, and such spasmodic contraction of the cerebral vessels appears to occur in many pathological conditions in which headache is a frequent symptom,—for example, in uræmia. It is, therefore, not improbable that the abolition of cerebral vascular spasm is responsible for the relief of the headache which often follows the use of the antipyretics in such cases.

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QUININE

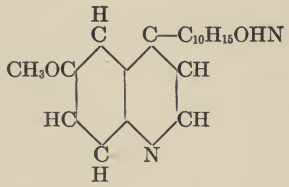
Cinchona bark is obtained from different species of cinchona which are natives of the highlands of western South America. Long used by the natives in malaria and other fevers, after the discovery of South America it was brought to Europe under the name of Jesuit's powder, and became known to the medical world about the end of the 17th century.

While formerly obtained from various wild varieties of the cin-

chona tree, it is now chiefly obtained from a dwarf variety, Cinchona succirubra, which is cultivated on a large scale in Java and the East Indies. This bark contains more than 20 alkaloids, the so-called cinchona bases, of which, besides quinine, only quinidine, cinchonine, and chinchonidine need be mentioned. The official bark must contain 5 per cent. of alkaloids.

While the bark is still much used in the form of extracts and tinctures as a bitter (see p. 167) and tonic (see p. 404), in the treatment of fever it has been entirely replaced by quinine, first prepared by *Pelletier* and *Caventou* in 1820.

Quinine, $C_{20}H_{24}N_2O_2$, occurs in the bark in combination with quinaic acid and quinotannic acids. Its structural formula is probably as follows:



Of the various water-soluble and intensely bitter salts, the **hydrochloride** is the most useful. It is soluble in 30 parts of water, but the addition of urea, urethan, or antipyrine renders it soluble in equal parts of water. The **sulphate** is soluble in 800 parts of water, and the **bisulphate** in 12 parts, its solutions having an acid reaction.

Various insoluble preparations are more or less used, because, being insoluble, they are also tasteless or almost so. It should be remembered, however, that their insolubility renders their absorption slow and uncertain. Of these the more widely used ones are **quinine tannate, equinine** (quinine ethyl carbonate), $CO(O.C_2H_5)(O.C_{20}H_{23}N_2O)$, and **aristochin** (diquinine carbonic ester), $CO(OC_{20}H_{23}N_2O)_2$, which, on account of their lack of taste, are frequently administered to children.

Quinine is unequalled by any other substance as a specific for malaria, and is also used in the treatment of neuralgia, whooping-cough, and other conditions. As an antipyretic in other infectious diseases, it possesses advantages only in those (typhoid, septicæmia, influenza) in which, with more or less justification,* specific effects may be attributed to it, or in cases where its long-continued use is indicated in order that its conservative action on the proteid metabolism may be of advantage. These advantages are, however, counterbalanced by its weaker antipyretic powers and by the disagreeable

* See footnote, p. 471.

"side actions" of larger doses, particularly on the central nervous system, even doses of 1.0 gm. at times causing cinchonism, with its symptoms of tinnitus, deafness, vertigo, headache, and vomiting. It may also act unfavorably on the alimentary canal, the continued use of even small doses occasionally causing various types of indigestion. Skin eruptions also not infrequently follow the administration of quinine. Toxic doses cause more or less persistent deafness and serious disturbances of the vision, even permanent blindness, and very large doses may cause stupor, coma, and collapse as a result of depression of the central nervous system and of the heart.

While the greater portion of quinine is combusted or otherwise decomposed in the organism (*Nishi*), a portion is excreted unchanged by the kidneys, the urine acquiring an emerald-green color on the addition of chlorine water and ammonia, a reaction characteristic of quinine solutions.

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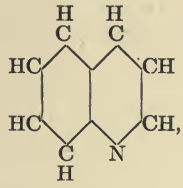
ANTIPYRINE GROUP

In the endeavor to obtain substitutes for quinine, the start was made by searching for the active nucleus of quinine.

While *quinoline,*



one of its decomposition products, acts as an antipyretic and powerful narcotic, it so readily causes collapse that it could not be used in practice. However, in 1883, by the introduction of side chains into quinoline, the first useful synthetic antipyretics, *kairine* and *thallin,* were obtained; but these also acted too violently, for, although after their administration the temperature falls rapidly with profuse sweating, it rises again after a comparatively short time, this rise being not infrequently accompanied by a chill.

In 1884 *Knorr* prepared and recognized the antipyretic powers of **antipyrine,** a pyrazolon derivative, and in 1887 the therapeutic properties of **acetanilide** were discovered. While the antipyretic action of its mother substance, aniline, had been recognized by *Schuchardt* in 1861, this discovery had remained unnoticed. Although aniline itself is powerfully toxic, the discovery of acetanilide indicated that among its derivatives and those of the closely related paramidophenol there were certain relatively non-toxic and promptly acting antipyretics.

The antipyretics belonging to this pharmacological group may, from a chemical point of view, be divided into the aniline and paramidophenol derivatives and the substances of the pyrazolon group.

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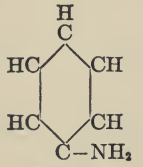
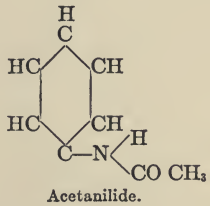
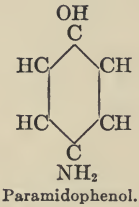
I. ANILINE AND PARAMIDOPHENOL DERIVATIVES

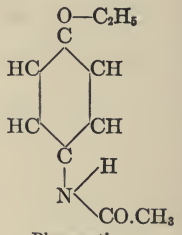
Although these mother substances are powerfully toxic to nervous cells, and although in larger doses they cause the formation of methæmoglobin, their toxicity may be diminished by the introduction of various side chains. Paramidophenol is less toxic and more antipyretic than the ortho- and meta-modifications, which are less powerful antipyretics and at the same time are more destructive to the blood.

After large doses of these substances the urine often becomes dark colored and, on account of the presence in it of paramidophenol, gives the indophenol reaction—*i.e.*, on the addition of hydrochloric acid and sodium nitrate followed by an alkaline solution of naphthol and then by NaOH, acquires a red color, which on acidification changes to violet.


Aniline.


Acetanilide.


Paramidophenol.


Phenacetin.

Acetanilide (antifebrin), obtained from aniline by replacing one hydrogen atom of the amido group by an acetyl radical, occurs as a crystalline bitter substance, soluble in 230 parts of water. It is a prompt and powerful antipyretic and analgesic, of which the dose is 0.2 to 0.3 gm. per dose. In former times, as a result of exceeding the proper dosage, numerous cases of poisoning occurred, which were characterized by cyanosis of the face and blueness of the hands and fingernails, effects of the formation of methæmoglobin and the destruction of the blood-vessels (*Müller*). In more serious poisoning collapse also frequently occurred.

In the body, the nucleus of acetanilide undergoes oxidation, and it is excreted chiefly in conjunction with sulphuric and glycuronic acids as acetylparamidophenol (*Müller, Mörner*).

Phenacetin, acetphenetidin, is a paramidophenol, in which an ethyl radical has been introduced into the hydroxyl group and an acetyl radical into the amido group, and may, therefore, be termed an oxyethylacetanilide. It is a tasteless crystalline powder, which is very insoluble in water and more active [? Tr.] and less toxic than acetanilide. Doses of 0.25 gm. produce some antipyretic effects, while after 0.5 to 0.75 gm. the antipyretic effect is apparent after 30 minutes and lasts for 6 to 8 hours, usually unaccompanied by disagreeable side actions. In doses of 0.3 to 0.7 gm. it is a useful analgesic and sedative. After larger doses, such as 1.0 gm. per dose or 3.0 gm. per diem, cyanosis similar to that caused by acetanilide has been observed, but it rarely or never causes severe collapse.

Lactophenine, lactyl-para-phenetidin, is a phenacetin in which the acetyl radical has been replaced by the lactic acid radical. It is more soluble than phenacetin and has proven a useful antipyretic, possessing also considerable sedative powers. The maximum dose is 0.5 gm. per dose, 3.0 gm. per diem.

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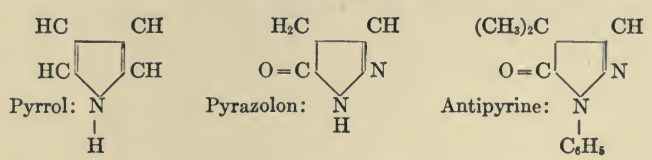
II. PYRAZOLON DERIVATIVES

ANTIPYRINE, phenyldimethylpyrazolon, is a derivative of pyrazolon, its constitution being illustrated by the following formula:



It is a colorless crystalline powder, with a neutral reaction and a very slightly bitter taste, which is soluble in equal parts of water. With ferric chloride it gives, even in very dilute solutions, a blood-red color, and with sodium nitrite an intense green color, due to the formation of nitroso-antipyrine. Following its administration, the urine is usually dark colored and acquires a reddish-purple color on the addition of ferric chloride. A portion is excreted unchanged, but the greater portion is excreted in conjugation with glycuronic acid as oxyantipyrine.

In doses of 0.4 to 0.8 gm. antipyrine is a certainly acting but rather mild antipyretic, the temperature usually falling during the course of 3 to 4 hours, accompanied by sweating, and rising again gradually. Alarming collapse, such as results from some of the more violently acting antipyretics, is observed after antipyrine no more frequently than with phenacetin. It is also very much used as a sedative and analgesic, the maximal dose being 1.0 gm. per dose and 3.0 gm. per diem.

Although even doses of 2.0 gm. very seldom cause any disagreeable effects, still certain individuals exhibit a striking idiosyncrasy to antipyrine. The most common undesirable effect is the occurrence of skin eruptions, which, while disagreeable, are not dangerous. It is only in the presence of idiosyncrasy that severer cutaneous manifestations occur, such as inflammatory swelling of the skin of the face and of the genital organs, as also symptoms of irritation of the mucous membranes, such as conjunctivitis, pharyngitis, laryngitis, etc., and occasionally pronounced disturbances of the stomach (*Falk*).

Migrainine is not a chemical substance, but a mixture of antipyrine 85 parts, caffeine 9 parts, and citric acid 6 parts.

Salipyrine, phenyldimethylpyrazolon salicylate, is a coarse crystalline powder, soluble with difficulty in water, of which the dose is 0.5 to 1.0 gm.

Pyramidon, dimethylamido antipyrine, is a crystalline powder, only slightly soluble in water and almost tasteless. Its actions are similar to those of antipyrine, but it is 3 or 4 times as powerful [? Tr.], so that its dosage is correspondingly smaller (0.25 to 0.3 gm.). [Pyramidon, besides being an antipyretic and analgesic, is apparently also a fairly powerful hypnotic.—Tr.] After its administration, antipyryl urea and a red coloring substance, rubazonic acid, appear in the urine (*Jaffe*).

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III. SALICYLIC ACID GROUP

Although free salicylic acid is antiseptic and locally very irritant, sodium salicylate lacks these properties.

Sodium salicylate, a white hygroscopic powder, soluble in equal parts of water, acts in doses of 0.5 to 1.0 gm. as an antipyretic, but this action is not so elective as is the case with the above-mentioned drugs, and, if the dose be too large, symptoms of excitation of certain parts of the central nervous system and disturbances of the digestion readily appear. As undesirable side effects, it may cause dyspnœa and symptoms like those of cinchonism,—viz., deafness, tinnitus, vertigo, headache, and confusion,—and, if there be a pronounced fall of temperature, it relatively often causes collapse.

Those compounds of sodium salicylate, such as **salol** (phenyl salicylate), from which it is gradually set free in the intestine, cause these disagreeable side effects to a slighter degree, inasmuch as less salicylic acid reaches the circulation at one time. This is also true for **aspirin**, acetyl salicylic acid (see p. 472), at present widely used in place of the salicylate of soda. The antipyretic effects of aspirin also appear to be greater than those of salicylic acid, even doses of 0.25 gm. producing pronounced antipyresis in typhoid fever (*Bondi*).

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CHAPTER XVI

PHARMACOLOGY OF INFLAMMATION

NATURE OF INFLAMMATION

In its biological significance, inflammation may be looked upon as a reaction of damaged tissues, by means of which the damage is limited and such tissues as may be destroyed are removed and replaced. The essential process in this reaction is an alteration of the function of the vessel walls, affecting not only the smaller arterioles and veins but also the capillaries, as a result of which the vessels dilate, losing their tone and becoming permeable for both the plasma and the red and white blood-cells, so that transudation occurs (*Klemensiewitz*).

The first effect is an active hyperæmia, causing heat and redness, and the second an increased transudation into the perivascular and interstitial lymph-spaces, causing œdema or swelling. This œdema increases the tension in the tissues, and consequently causes stasis of the blood and stretching or twisting of the nerves, with tenderness and pain. Finally, the leucocytes and to a less extent the erythrocytes leave the inflamed vessels in large numbers, which leads to infiltration of the tissues, phagocytosis, and formation of pus, and also to cytolysis by the pus-cells, with a resulting dissolution and regeneration of tissues. For our purposes it is not necessary to go more deeply into these complex processes of inflammation; but it should be strongly emphasized that in general the reaction of inflammation is a useful process, and one necessary for the cure of the patient and for replacement of destroyed tissues, which, however, can itself work harm to the organism not only by causing violent pain but also by causing temporary or permanent functional disturbances, as, for instance, by the formation of large exudates or cicatrices or as a result of destruction of important tissues.

From such consideration it is clear that it will often be extremely desirable to be able to control inflammation either by stimulating or moderating its activity. Hence arises the demand for agents which stimulate and those which inhibit inflammation.

THE EXCITATION OR STIMULATION OF INFLAMMATION

The vasomotor disturbances which cause or initiate inflammation may be induced indirectly through the vasomotor nerves, or directly by the action of chemical substances on the vessels themselves. That inflammatory vascular disturbances, with all their sequelæ, may result from nervous influences, is proven by the occurrence of the different forms of herpes as the result of pathological processes in the spinal ganglia, as also by the occurrence of circumscribed hyper-

æmia or of vesicles, bullæ, etc., as a result of suggestion (*Heller u. Schultz*). Such lesions are in all probability always due to a peculiar primary stimulation of the vasodilator nerves, which causes first an active hyperæmia and later increased permeability of the vessels, leading to transudation, etc.

It is difficult to refrain from assuming in such cases that certain trophic functions of the vasomotor nerves, or perhaps specific trophic nerves, which respond only to certain adequate stimuli, also play a rôle in causing the inflammatory reaction, for inflammation never results from simple vasodilatation, such as follows experimental stimulation of vasodilator nerves in the skin or that caused by the functional activity of the organs.

In this connection it is of interest that these vasodilator nerves which accompany the spinal and some of the cranial nerves—*e.g.*, the trigeminus—appear to be identical with the sensory nerves which are interrupted in the synapses of the spinal ganglia (*Bayliss*). If this be actually so, the sensory nerves must transmit not only centripetal sensory impulses but also centrifugal vasodilator impulses, and, consequently, it must be assumed that their peripheral terminations are dichotomous, one twig passing to the cutaneous sensory corpuscles and the other into the smaller vessels. One is consequently tempted to assume the possibility of the passage of stimuli over a short path from algesic points to the smaller vessels, in analogy with an axon reflex. This assumption would explain why every painful irritation of the skin causes almost immediately a local active hyperæmia, the first stage of inflammation, and why, on the other hand, when the painful irritation of the skin is prevented, either by analgesic drugs or by cold, hyperæmia does not develop or is diminished, and with it also all other signs of inflammation (*Spiess*).

Bruce's studies indicate that these assumptions are well founded, for they show that, when inflammation is due to cutaneous irritation, it occurs even after section of the peripheral nerve-trunks, indicating that the reflex occurs independently of the central nervous system. Moreover, if the sensory nerve-endings be paralyzed by cocaine, alypin, or similarly acting drugs, irritation, which ordinarily causes inflammation, such as that caused by cantharidin when applied to the conjunctiva of a rabbit, produces no inflammatory reaction so long as the anæsthesia lasts, or none at all if the sensory nerve-endings have degenerated, as occurs within about eight days after section of the corresponding sensory nerves.

Consequently, drugs or other agents which when locally applied first cause more or less severe pain and resulting redness and inflammation are to be grouped together as indirect irritants. These correspond in general to those drugs or measures which are ordinarily termed

CUTANEOUS IRRITANTS OR RUBEFACIENTS

and include heat and numerous substances, particularly such as are volatile and readily penetrate the epidermis. Among the most important are oil of mustard, turpentine, chloroform, acids, ammonia, camphor, and iodine. The prolonged action of all these drugs and

of heat also, or their use in strong concentrations, besides irritating the sensory nerve-endings, can injure the tissues and can either cause inflammatory vasomotor changes or cause the death of various tissue cells. In such actions they resemble the members of the group of

SUBSTANCES WHICH DIRECTLY EXCITE INFLAMMATION

(*a*) *Specific vascular poisons,* substances which, without causing any destruction or necrosis of the tissues, act only on the vessels, perhaps also on the lymphatics, dilating them and rendering them abnormally permeable. These are certain toxic substances, probably proteid in their nature, which belong to the group of the so-called toxins. Among these may be mentioned tuberculin (*Pirquet*), diphtheria toxin (*Bingel*), abrin and ricin, the toxic substances of the pollen of certain graminaceæ, the hay-fever toxin (*Wolf-Eisner*), snake venoms, cantharidin, the toxic substances of the poison-ivy, Rhus toxicodendron (*Ford, Pfaff*), and of the primula, Daphne mezereum, the toxic substance in the bee's sting (*Langer*), and the Kalahari arrow-poison (*Starcke*). These substances all cause active hyperæmia and serous infiltration of the tissues. Those which are able to penetrate the skin when applied to it cause papules or vesicles containing leucocytes and often large numbers of red cells.

These substances possess the common characteristic that certain individuals or species of animals are entirely or relatively immune to them, their action being dependent on a specific disposition of the individual or species, the nature of which is still almost entirely unknown. Such disposition may be either positive or negative, manifesting itself as a specific susceptibility or a specific insusceptibility of the organism to a certain poison. In many cases this disposition is changeable, but in others it is constant.

Tuberculin excites a distinct cutaneous reaction only in individuals who are or who have been infected with tuberculosis, and a decidedly more pronounced reaction in the tubercular tissues than in the non-tubercular ones. The same holds good for reactions to other toxins and heterologous sera (*v. Pirquet*).

Cantharidin also acts more strongly on tubercular lesions than on normal tissues. On the other hand, the tissues of many species of animals (hedgehog, chicken, frog) are in a high degree immune to it. Contact with poison-ivy and the primula obconica (*Wechselmann*) causes erythema and vesication only in susceptible individuals. Snake venom, abrin, ricin, and poison-ivy are harmless to the skin of cold-blooded animals, but on human skin they are very poisonous, snake venom only when the epithelium has been injured, but abrin and ricin through the uninjured cutis. However, in man repeated mild poisoning with them leads to an immunity, which probably is entirely distinct from the natural immunity of the cold-blooded animals.

(*b*) *Caustic and Necrotizing Agents.*—A very large number of substances possess in common the power of killing all living protoplasm alike. These are either substances causing instantaneous destruction—as is the case with trauma, glowing heat, and corrosives of all kinds, such as concentrated acids and alkalies—or substances, such

as arsenic, which cause necrosis by more delicate but nonreversible and therefore progressive molecular actions which gradually cause the death of the tissues.

Whether rapid or slow, the death of the tissue cells under all conditions causes a chemical decomposition of protoplasm, with a resulting formation of decomposition products, just as occurs in the fermentative post-mortem autolysis of organs. These decomposition products possess in a high degree the power of exciting inflammation,—*i.e.*, they produce the essential vascular changes and chemotactic assemblage of leucocytes. Apparently they irritate or render more irritable the algesic nerves, and perhaps they also furnish a stimulus for the growth of regenerating tissues.

The augmentation of the susceptibility to pain by inflammatory products is especially strikingly demonstrated in the visceral peritoneum, whose algesic nervous mechanism ordinarily responds only to stimuli resulting from extreme distention, but which in peritonitis responds to every slightest mechanical—and presumably also to every chemical—irritation.

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CLASSIFICATION

Substances and agents which excite inflammation may consequently be divided into three groups, which, however, cannot be sharply differentiated from each other.

1. Painful cutaneous irritants, the **rubefacients.**

2. Vascular poisons, the **vesicants** and **pustulants,** which, when applied to the skin, cause vesication and pustulation, and when applied to the mucous membranes cause hyperæmia, œdema, and formation of pus.

3. Cytotoxic agents, **caustic** and **necrotizing** agents.

THERAPEUTIC EMPLOYMENT AND MODE OF ACTION

Formerly these agents were used locally as derivatives and epispastics, with the idea that by their action on the surface a deep-

seated inflammation could be brought to the surface. At that time, however, there was no satisfactory explanation or knowledge of the manner in which counterirritation produced its beneficial results.

To-day their mode of action is no longer so incomprehensible, since *Bier* has shown that passive hyperæmia of an organ—*i.e.*, a hyperæmia resulting from primary vasodilation—is a condition of essential moment for the protective reactions of inflammation and also of importance for the relief of pain. It has also been shown that irritation of the skin causes hyperæmia not only superficially but, according to its severity, in more or less deep-lying as well as in more or less distant parts, and even in organs which are in no way directly connected with the skin; for instance, in the thoracic and abdominal viscera and in the dura, in which latter cases it is evident that the hyperæmia must be reflexly induced. *Head* has shown that inflammation of the different viscera often causes a hyperæsthesia or hyperalgesia of those portions of the skin which are innervated from the same segments of the cord to which the sensory nerves of the viscera in question pass, and that there is a definite reflex sensory relationship between the viscera and the skin. It would, therefore, appear more than probable that an irritation from without may produce effects on the related viscera and cause a hyperæmia, and, as a matter of fact, it is possible experimentally to demonstrate that this is the case.

It is thus evident that the term **derivative** as used in connection with the counterirritants is a misnomer, for they do not deprive the organs of blood, but, on the contrary, augment their blood supply, and thus under certain conditions may exert a favorable influence on the process of healing or repair.

In addition, sensory irritation, according to its severity, reflexly stimulates or depresses (inhibits) the circulation and the respiration. Thus, the respiration is stimulated by mechanical or chemical stimulation of the trifacial nerve-endings in the nasal mucosa, or by cold douching of the neck or breast and by other similar procedures (see p. 341). Very violent cutaneous irritation, such as that which may be produced by mustard or cantharides, diminishes the respiratory exchange in rabbits, but thus far this question has not been sufficiently investigated in man (*Mayer*).

Mild cutaneous irritation appears to produce an opposite effect, increasing both the depth of respiration and the respiratory exchange (*Rubner, Winternitz, Loewy u. Müller, Matthes*).

The vasoconstrictor centres are stimulated even by weak sensory stimuli, and the vasodilator and vagus centres by powerful ones. While these reflexes, although of great importance both for physiology and therapeutics, cannot be discussed further in this place, it should be mentioned that they play an important rôle in physical therapy, particularly in hydro- and electrotherapy (*Müller*).

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CUTANEOUS IRRITANTS OR COUNTERIRRITANTS

Almost all volatile "lipoid-soluble" substances cause sensory irritation and rubefaction, for they readily penetrate through the skin and its fatty layer and into the sensory nerve-endings.

Carbon dioxide in the carbonic acid baths, dilute **alcohol** (20–40 per cent.), and **chloroform** (with an equal amount of olive oil) act in this fashion.

Another widely used counterirritant is **turpentine**, which is obtained by the dry distillation of the resins of the different coniferæ and which is an ingredient of many plasters, etc., used as cutaneous irritants.

It is a mixture of pinene, $C_{10}H_{16}$, with small amounts of other terpenes and traces of organic acids. Rectified spirit of turpentine is obtained by distilling the crude product with lime.

When left in contact with the skin for a time, it causes redness and burning of the skin, while on longer contact it penetrates more deeply and causes vesication and pustulation. It irritates the gastric and intestinal mucosæ but slightly, so that 1.0 gm. or more may without injury be taken several times daily. It is readily absorbed and is excreted through the kidneys, in part unchanged and in part as terpene alcohol in conjugation with glycuronic acid, the urine acquiring some antiseptic power and an odor resembling that of violets.

The terpenes and resinous acids of **copaiba, cubebs,** and **sandalwood oil** also render the urine feebly antiseptic as well as astringent, for the resinous acids excreted in it precipitate albumin (*Vieth*). These actions account for the favorable effect of these drugs in inflammations and infections of the lower portion of the urinary tract.

In order to avoid irritation of the stomach and intestines, it is best to employ for this purpose the salicylic ester of the oil of sandal-wood (santyl) or esters of terpene alcohols, which are non-volatile and very slightly irritant. These drugs, however, during their excretion can cause inflammation of the renal capillaries, just as they do in the skin, dilating them and rendering them more permeable, so that diuresis is augmented, and at times albuminuria and hæmaturia may result from their administration. [Probably only when large doses are taken or when the kidney is already damaged are these drugs likely to cause any serious renal injury, but this action should be borne in mind when considering their use in large doses or in nephritic cases.—Tr.]

Oil of Juniper.—The essential oil of Juniperus sabina, a mixture of the alcohol, sabinol, and of various terpenes, is extremely irritant to and often

causes necrosis of the kidney epithelium, as well as elsewhere. Taken internally it causes gastro-enteritis, hæmaturia, and marked hyperæmia of the pelvic organs, and even abortion. Externally it is employed as an ointment for the gradual removal of polypoid growths, etc. [It is present in gin.—Tr.]

A small portion of the turpentine absorbed (also of cubebs, copaiba, and oil of sandal-wood) is excreted through the lungs, and may act as a disinfectant and deodorizer in purulent bronchitis or in gangrene of the lung. In addition turpentine, particularly when inhaled, diminishes the bronchial secretions, and may be consequently used with advantage in certain cases of bronchitis.

Camphor, $C_{10}H_{16}O$, in alcoholic or oily solution, may be used as a mild counterirritant.

Arnica, which is widely used by the laity, contains arnicine, a substance which causes cutaneous irritation.

Acetic and **formic acids** in various dilutions may be used for similar purposes, as is

Ammonia, which is an ingredient of various liniments, and which is also used in smelling salts as a means of reflexly stimulating the respiratory and vasomotor centres.

When concentrated ammonia is respired, it immediately causes burning pain, a reflex spasmodic closure or œdema of the glottis, and violent irritation with swelling and exudation in the laryngeal and tracheal mucous membranes. Strong aqueous solutions, when left in contact with the skin, cause within 15 minutes severe burning, redness, and vesication.

Dilute alkalies, such as solutions of potash or soda or alkaline soaps, especially sapo mollis, in pure form or as the tincture, produce the same effects. Aqueous solutions of the alkaline carbonates or of soaps emulsify the cutaneous fats and facilitate their removal, and with prolonged action loosen the superficial layers of the skin and reach the sensory nerve-endings, causing burning or pain.

The **alkaline sulphides** are more powerfully irritant, for they soften and dissolve the keratin of the epidermis and consequently readily penetrate it. Sulphur itself, when applied in salves or pastes, exerts similar but much weaker actions, for in contact with the skin it is gradually transformed into alkaline sulphides (p. 209). When a paste of calcium sulphide, prepared by the action of H_2S on milk of lime, is rubbed on a hairy part, it acts as a powerful depilating agent, and is actually used in the Orient as a substitute for the razor.

Substances insoluble in the lipoids, such as most of the indifferent salts, do not penetrate the skin in appreciable amounts unless they penetrate into the sebaceous glands,* where they may be absorbed by the living epithelial cells, or unless the skin has been rendered more permeable by prolonged warm baths or poultices. Previous removal of the cutaneous fat, by ether, alcohol, or chloroform, facilitates the absorption of such salts (*Winternitz*).

* Such substances are consequently not absorbed when applied as ointments unless they are driven into the skin by prolonged and vigorous friction.

Salt Baths and Sea Baths.—None of the constituents of such baths are directly absorbed by the skin, except in so far as a certain amount remains on the skin and, as a result of friction, is gradually driven into the glands and between the epithelium. During this process they cause a mild but often very lasting stimulation of the skin, with a resulting redness and feeling of warmth, effects which may reflexly produce a stimulation of the nervous system and metabolism.

Iodine is a very efficient counterirritant and one especially adapted to cause sharply limited or readily modified counterirritation. For this purpose it is employed in the form of its tincture (7 per cent. in alcohol) or as Lugol's solution (5 per cent. I, 10 per cent. KI in water).

As iodine is volatile at ordinary temperature, it does not long remain on the exposed surface of the skin, so that its deep brown stains quickly fade to a light yellow. Its local application is followed by a feeling of warmth and prickling and by a hyperæmia of the skin. Prolonged or frequently repeated application may cause the development of large blisters. The hyperæmia and serous infiltration caused by it may extend quite deeply into the tissues and result in a cytolytic dissolution and absorption of diseased tissues or of pathogenic material. Iodine is consequently a favorite agent for the treatment of inflammatory tumors, swollen glands, arthritis, etc. Solutions of iodine may also be injected into cysts, hydroceles, etc., after they have been emptied, to cause inflammatory reactions leading to obliteration of such cavities. If, however, too large amounts are thus injected, serous poisoning may result from the iodine which is absorbed, and which is eliminated by the alimentary mucosa and by the kidneys, causing violent gastro-enteritis with persistent vomiting, serous exudates into the pleural cavity, nephritis, and profound coma (*Rose*).

Solutions of iodine act much more powerfully on mucous membranes than on the skin, and cause destruction of the superficial layers and intense hyperæmia of their lower layers. As the sensory nerve-endings in the mucosa are benumbed or killed, the points of application remain for some time benumbed and almost insensitive.

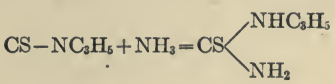
Oil of Mustard is also a member of this group of cutaneous irritants.

It is formed by the action of a ferment on potassium myronate (sinigrin), $C_{10}H_{18}NS_2KO_9$, which is contained in the seeds of Brassica nigra, and which is decomposed hydrolytically into the oil of mustard, isosulphocyanallyl, $CSNC_3H_5$, dextrose, and potassium bisulphate. This ferment, myrosin, is contained in the mustard seeds and becomes active when the pulverized seeds are moistened with water. [As this ferment is destroyed by heat, care should be taken when making poultices that the water be not too hot, otherwise the ferment is destroyed and as a consequence the mustard's activity is more or less completely destroyed.—Tr.]

This oil has an extremely irritant odor, and when applied to the skin causes burning and redness, and, if sufficiently concentrated or

if the action be prolonged, causes vesication. It is used as a cutaneous irritant either in the form of a mustard plaster or leaf, in which form its action develops gradually, producing a gradually increasing irritating effect, or as a liniment in the form of a tincture or spirit of mustard, in the strength of 2 parts to 100.

Care should be taken not to permit it to cause more than pronounced redness of the skin, for experience has shown that the blisters caused by it heal very slowly. The simultaneous application of preparations containing ammonia has also to be avoided, for ammonia and mustard oil readily combine to form thiosinamine with the formula



FIBROLYSIN.—THIOSINAMINE, or allyl sulphocarbamide, when combined with sodium salicylate is known as fibrolysin. When applied to the skin it produces no effects, but when injected subcutaneously—thiosinamine best in 15 per cent. alcoholic solution, fibrolysin best in an aqueous one—it causes severe pain and hyperæmia, and after absorption causes, it is claimed, a thus far unexplained softening and absorption of the connective tissue of scars and other connective-tissue growths. It has consequently been recommended as a means of bringing about the softening of cicatricial contractures in the extremities and of strictures, —for example, strictures of the œsophagus. *Teleky* states that under its influence fresh adhesions, such as those following laparotomies, fistula operations, etc., readily loosen up, an effect which may be distinctly undesirable.

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VESICANTS AND SUPPURANTS

Of the various substances which may cause vesication, only three are actually used in medicine, the Spanish fly or cantharis, Daphne mezereum, and the fruit of Anacardium occidentale.

Cantharides.—Although their common name is Spanish flies, these are neither Spanish nor are they flies, but beetles, from 2 to 3 cm. long, of an emerald-green color, which are distributed throughout both hemispheres in the tropical and temperate zones. Their bodies contain an acid lactone, **cantharidin,** which is insoluble in water, but readily soluble in fats, ether, and alcohol, and to which they owe their activity. A number of other allied species also contain cantharidin.

Cantharidin is applied to the skin in the form of a plaster, ointment, or collodion, either to cause a local reddening or hyperæmia or to cause vesication. Its application is quite quickly followed by a reddening of the skin and pain, and after some hours the epidermis is raised from the corium and a blister containing serum and many leucocytes is formed, by which time the pain and the redness have

disappeared and the corium has become pale. When the blister is emptied, the epidermis reforms rapidly, as a rule, and the blister heals promptly, but, if cantharidin be again applied to the exposed corium, violent purulent inflammation may result.

When swallowed in small amounts, such as 0.5 c.c. of the tincture, it causes only a feeling of warmth in the epigastrium; but large doses may cause violent gastro-enteritis, swelling of the submaxillary glands, and active salivary secretion and nephritis. When very small doses are repeatedly administered or when small quantities of cantharidin are repeatedly applied to the skin, as a result of the absorption of the cantharidin a severe glomerulo-nephritis, and, under some conditions, a violent irritation of the urogenital tract, with frequent painful micturition and hyperæmia and sensory irritation of the genital organs, may occur. These last effects account for the formerly not infrequent abuse of cantharides as an abortificient and as an aphrodisiac.

The kidney lesions appear to be dependent on the reaction of the urine, for, according to *Ellinger*, cantharidin causes only a slight albuminuria in rabbits as long as the urine is alkaline, but, if this becomes acid, causes a very violent hemorrhagic nephritis, which may prove fatal. **Consequently, with threatened cantharidin poisoning in man the administration of alkalies would appear to be indicated.**

Cantharidin, being a lactone, combines in the presence of water with alkalies, forming soluble salts. Sodium cantharidinate has been employed, on *Liebreich's* recommendation, in the presence of already existent inflammation, to increase the permeability of the smaller blood-vessels, with the idea of causing more pronounced serous infiltration with its often curative effects. When thus employed, it is administered subcutaneously in very dilute solution (1: 10,000), and, while curative effects have been obtained by its use in such conditions as lupus, such administration has often caused renal irritation, so that its use has been abandoned.

The dried bark of **Daphne mezereum** has been employed as a household remedy as a vesicant and suppurant. **Cardol**, a very irritant oil obtained from husks of Anacardium occidentale (cashew-nut), was also formerly employed as a vesicant.

Almost all of the other vesicants and suppurants mentioned in the introduction do not penetrate the intact epidermis, but produce their harmful effects on the vessels only when applied to open wounds or to mucous membranes, or when absorbed from subcutaneous tissues or from the alimentary canal.

Abrin and **tuberculin** are the only ones of them which are at present of practical importance. The former is a toxic substance, probably of proteid nature, contained in the seeds of Abrus præcatorius, which when applied to mucous membranes causes a more or less violent purulent inflammation, and which is at times employed in ophthalmological practice (see p. 160). Concerning tuberculin the reader is referred to page 545.

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ESCHAROTICS OR CAUSTICS

These are used not to cause a healing inflammation, but to destroy pathological tissues. Such destruction is produced instantaneously by the action of such powerful chemical substances as the caustic alkalies, concentrated acids, and certain of the salts of the heavy metals.

THE CAUSTIC ALKALIES, fused caustic potash, etc., dissolve proteid and keratin, with the formation of a viscid water-soluble mass, through which the caustic penetrates further, so that its painful caustic action is not sharply limited. By the addition of the less soluble lime, it is possible to limit somewhat the depth and extent of this caustic action.

ACIDS.—*Lactic acid* also dissolves proteid and keratin, and consequently its caustic action is not sharply limited and is rather persistingly painful. However, as healthy cells are relatively resistant to it, it may be employed to electively destroy pathological tissues.

Of the other acids, fuming *nitric acid* and *trichloracetic acid* are the ones most used as caustics, as both of these form from the destroyed tissues a firm leathery eschar. It is possible to produce with them a cauterization which is sharply limited and accompanied by pain of but short duration. The eschar caused by nitric acid has a lemon-yellow color, due to the nitrified proteid (xanthoprotein); that produced by concentrated aqueous solutions of trichloracetic acid is white.

Chromic acid, CrO_3, which occurs as red crystals readily soluble in water, is a very powerful caustic, formerly much used, but now abandoned because too poisonous.

METALLIC SALTS.—Those salts of the heavy metals which are hydrolytically dissociable act as caustics in the same fashion as, although more weakly than, the free acids, precipitating proteid, with the formation of acid albuminates and metal albuminates, and thus destroying all protoplasm. They are employed either in pure form as caustic pencils, in concentrated watery solution, or in the form of pastes.

If all the constituents of the protoplasm are not equally affected chemically by a substance, but if only certain of them are thus acted upon, the cell is not necessarily destroyed, but only damaged and, in certain cases, gradually killed. Thus, for example, the mere disturbance of the osmotic condition of a cell may bring about its death and decomposition, particularly if its vitality is already depressed. In such fashion pure water, by diminishing the osmotic tension of the superficial cells of the gastric mucosa, may kill them and thus favor the regeneration of new cells, while concentrated salt solutions, pure glycerin, etc., may produce similar result by augmenting their osmotic tension.

Arsenic, in the form of arsenic trioxide, a white tasteless powder, soluble with difficulty in water, is a most certain means of bringing about the gradual death of cells. When applied to wounds or mucous membranes, it does not directly cause a sensory or inflammatory irritation, but those cells which have come in contact with arsenic in solution gradually die and after some days undergo necrotic decomposition. In this fashion it may cause destruction of tissues to a considerable depth. It is employed with good results in dentistry as a means of killing and destroying the nerves in decayed teeth and their roots.

Antimony oxide also causes cell necrosis in quite the same fashion. The most important antimonial compound is tartar emetic, in which, however, the antimony does not exist as a free ion Sb''', but as the ion SbO' which apparently has no direct toxic actions. This salt is decomposed by acids, with the formation of the acid $Sb(OH_3)$, or the oxide Sb_2O_3, both of which are directly active. Consequently, salves or pastes containing tartar emetic, when applied to the skin, cause necrosis only in those places where it is decomposed by an acid secretion and changed into an active form,—*i.e.,* only in the mouths and the follicles of the cutaneous glands, in which small areas of necrosis are produced, forming pustules resembling those of variola.

Enzymes.—Certain digestive enzymes, such as *trypsin* and *papain,* a proteolytic ferment obtained from *Carica papaya,* have also been used to bring about a gradual destruction of pathological tissues.

THE INHIBITION OF INFLAMMATION

Inasmuch as inflammation is reflexly excited, or at least markedly augmented, by sensory stimuli, it follows that inflammation will be more or less inhibited by all agents which diminish or prevent sensory stimulation at the seat of inflammation. Further, all agents which prevent the abnormal dilatation and permeability of the vessels, and all which diminish the motility of the leucocytes, will also tend to prevent or lessen inflammatory reactions; and, lastly, inflammatory processes may be etiotropically combated by removing or rendering harmless the pathogenic agents causing the inflammation.

In accordance with the above, antiphlogistic agents, or agents restraining inflammation, may be grouped under the three heads of analgesic, astringent, and etiotropic agents. The last of these will be discussed in another chapter.

1. ANALGESIC ANTIPHLOGISTIC AGENTS

One of the most frequently used of these is **cold,** obtained by the local application of ice-bladders, etc. It goes without saying that the effect of cold in slowing the circulation, paralyzing the leucocytes, and constricting the vessels aids in controlling the inflammation.

Spiess in particular has called attention to the use of analgesics in

controlling inflammation. As emphasized by *Bruce*, agents used for this purpose should produce a somewhat lasting local analgesic effect, and should consequently be such as will not be dissolved and absorbed rapidly, for otherwise they would leave the place of application too quickly. Consequently, only rather insoluble ones, such as **anæsthesin** (p. 134), are adapted for this purpose, or they must be applied in large amounts in case they are sufficiently nontoxic. An example of the latter type would be alcohol, with which a dressing for a paronychia is saturated. In the case of the much-used chemically indifferent protective agents, such as gum arabic, starch paste, indifferent salves, plasters, and dusting powders, the favorable effects on the inflammation are undoubtedly chiefly due to their power of shielding the parts from chemical or mechanical sensory irritation.

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2. ASTRINGENTS

As has already been stated (pp. 212, 213), astringents form a more or less firm and impenetrable coating on the surfaces of wounds of mucous membranes by coagulating the superficial layers of cells, so that the glands and lymph-spaces are partially blocked, while the gland-cells themselves are altered and their secretions checked (*Schütz*) so that the parts become dry. They also become pale and constricted, because the smaller vessels are constricted and their walls rendered less permeable, and, consequently, the serous infiltration of the tissues and the emigration of the blood-cells is lessened or entirely prevented (*Heinz*).

Moreover, it must not be forgotten that the astringents also exert some etiotropic actions, as they act on the exciters of inflammation, killing pathogenic microbes, and, what is probably even more important, precipitating or destroying the inflammatory cytolytic ferments and those substances which are formed during every cell necrosis and which have the power of exciting inflammation. With the removal of these phlogogenetic substances, the irritation of the sensory nerve-endings and the pain both decrease, so that in this fashion the astringent may also relieve pain. In this particular the astringents show a certain resemblance to the etiotropic antiseptics, which will be discussed in a later chapter.

The chief members of this group are the various tannins, some of the salts of the heavy metals and of aluminum, and calcium hydroxide.

It is hardly necessary to state that numerous organic substances, such as **picric acid**, which precipitate and harden proteid, produce an astringent effect, but, on account of other properties, such as toxicity, volatility, etc., are practically ill adapted for such employment. Among them mention may hereby be made of **formaldehyde**, which may be used in dilute solution (1 to 10 per cent.) to harden the skin and to prevent localized excessive sweating.

In a former chapter sufficient has already been said about the various **tannins** (page 214 ff.), and in the same place **bismuth subnitrate** and **subgallate,** the **subacetate** and **acetate of lead, silver nitrate,** and **lime water** have all been discussed.

All the caustics mentioned above, which form a firm and tough eschar, when used in high dilution act as astringents, so that, even in the case of a cauterization, such as that produced by silver nitrate, the traces of the caustic agent which penetrate into the underlying tissues act there as astringents. Consequently the curative effects of many of these substances depend on such a combination of their caustic and astringent actions.

Of such caustics the most important practically are **silver nitrate,** the **sulphates** and **acetates of copper, alum** and **zinc,** and the **liquor ferri sesquichlorati.** The latter is also employed as a means of checking bleeding, on account of its power of causing coagulation of the blood.

If such caustics do not form solid compounds with the tissues, but, like the salts of mercury, arsenic, and antimony, form only soft or water-soluble products, they produce no astringent effects whatever. On the other hand, the caustic action is very slight or entirely absent in the case of those substances which, on account of their slight solubility in water or their slight power of diffusion, are able to produce only a weak and extremely superficial chemical reaction. In addition to the tannins, the following are examples of such substances: **Zinc oxide, lead oxide, lead carbonate, lead subacetate,** and the **subnitrate, subgallate,** and **subsalicylate of bismuth.**

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Bismuth Salts.—While the subgallate and subsalicylate of bismuth possess the advantage over the subnitrate that, when administered internally, they cannct cause nitrite poisoning,* they are inferior to it in that neither gallic nor salicylic acids are astringents.

Although the basic bismuth salts are insoluble in water, and cannot be absorbed in appreciable amounts either by mucous membranes (even inflamed ones) or by granulating wound surfaces, still, when brought in contact with fresh wounds, they without exception are transformed into soluble compounds of unknown character, which are absorbed, and consequently under these conditions they may cause serious

Bismuth Poisoning.—This very closely resembles subacute mercurial poisoning, and is characterized by the formation of dirty, dark-colored ulcerations in the mouth, particularly where the tongue or the gums are eroded, and by extensive necrosis in the large in-

* See p. 216.

testine, and also by glomerulo-nephritis (*Kocher, Mahne*). The ulcerations in the mouth and the large intestine result from the intracellular and intravascular precipitation of the oxide of bismuth by hydrogen sulphide (*H. Meyer u. Steinfeld*).

All other bismuth compounds, such as *xeroform* (bismuth tribromophenol), *orphol* (bismuth β-naphthol), *airol* (bismuth iodosubgallate), etc., may produce toxic effects, and it is consequently entirely incorrect to state, as is too often done, that any bismuth compound is absolutely non-toxic.

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Aluminum Salts.—The above is also true for the salts of aluminum, for they too are toxic if absorbed (*Siem*). Aluminum subacetate and dilute solutions of alum, aluminum sulphate, *alsol* (A. acetotartrate), and *aluminol* (A. naphtholsulphonate) are all used as astringents.

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Lime Salts.—In a former section (p. 217) the manner in which lime water acts as a local astringent has been explained, and also its superiority, for certain cases, to all other acid-reacting or insoluble astringents, owing to its power of dissolving mucus. This property is of particular value in the treatment of diphtheritic inflammation of the throat, in which thick pseudo-membranes containing much mucin are formed (*Harnack*).

The neutral-reacting calcium chloride, however, may also in a certain sense be considered an astringent, and a remotely acting one at that. In animals, in which the total amount of calcium has been increased by the subcutaneous injection of calcium chloride, inflammation does not occur at all or only in a mitigated form.

In such animals the instillation of oil of mustard or of abrin into the conjunctiva is not followed by the usual pronounced hyperæmia, chemosis, and pus formation, and pleural and pericardial effusions also fail to result from certain injections and poisonings which ordinarily cause them (*Chiari*), while the development of exanthemata is prevented or at least rendered very difficult (*Wright, Luithlen*). It appears, therefore, that calcium acts on the smaller blood-vessels, and perhaps also the lymph-vessels, so as to render them less permeable to the blood plasma and cells.

These effects are produced most certainly by subcutaneous injection and last about 24 hours, but they may also follow oral administration, although more slowly and in slighter degrees. In man 100 c.c. of a 2 per cent. solution of chloride of calcium may be taken internally (*Leo*), but only dilute solutions (1–2 per cent.) should be administered subcutaneously, as more concentrated ones cause necrosis at the point of injection. It must also be emphasized that calcium salts are by no

means non-toxic, for animals, into which 0.3 to 0.4 gm. $CaCl_2$ per kilo have been injected subcutaneously, die in a few days as a result of a central paralysis.

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Epinephrin acts in a different fashion, but also prevents inflammation. As is well known, when subcutaneously or intravenously administered, it markedly delays the absorption of chemical substances from serous cavities and from the subcutaneous tissues, probably on account of the persistent contraction of the blood and lymph capillaries (*Meltzer, Exner*).

As shown by recent experiments of *Fröhlich*, this vasoconstriction also prevents inflammatory transudation, for, after the intravenous injection of the more persistently acting and less toxic *d-epinephrin*, the oil of mustard does not cause inflammation of the rabbit's conjunctiva.

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Quinine may also in a certain limited sense be considered a substance possessing the power of inhibiting inflammation, for it diminishes the motility of leucocytes and thus prevents their diapedesis, as proven by the observations made by *Binz* on the inflamed mesentery of the frog. It is consequently not impossible that threatening formation of pus may be prevented by the internal administration of quinine, or that purulent foci already extant may be prevented from spreading (*Binz*).* In purulent catarrhal inflammations of the upper air-passages, large doses of quinine, according to common experience, exert an inhibitory influence on the inflammation. This may justify the presence of quinine as a constituent of various coryza tablets.†

According to *Winternitz*, ethereal oils also, after their absorption into the blood, have the power of limiting the formation of exudates in inflamed tissues and of favoring their absorption.

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* Satisfactory experimental and clinical proof of such action is, as far as the translator knows, still lacking.

† [Inasmuch as these tablets contain only small amounts of quinine it is probable that such effects as they produce are due entirely to the atropine which almost all of them contain.—Tr.]

CHAPTER XVII

ETIOTROPIC PHARMACOLOGICAL AGENTS

In so far as drugs alter the functions of the various organs in the body they may be looked upon as acting organotropically. In contrast to these is a group of drugs with which we are able to influence the causative agents of disease without producing essential changes in the functions of the various organs, and which may consequently be called etiotropic drugs. The causes of disease against which they direct their activity may be animate or inanimate,—*i.e.*, parasites, bacteria, protozoa, etc., or poisons, such as the so-called toxins.

Outside of the body the destruction of bacteria is attained by the use of disinfectant drugs and various physical agents, particularly heat. On the surface of wounds, mucous membranes, etc., bacteria may be combated by antiseptics, while against the animal parasites of the alimentary canal the antiparasitics are used. In such cases etiotropic drugs come in contact with the pathogenic organisms not inside of the tissues but on the surface of the higher organism, while in other cases it is possible to destroy the disease-producing organisms (protozoa) in the tissues themselves without essentially disturbing the organic functions of the body of the host. This we call specific antiseptic therapy.

If poisons taken into the stomach are rendered harmless by the proper antidotes,—for example, phosphorus by copper sulphate, arsenic by calcined magnesia,—the antidote really acts on the cause of disease in a fashion analogous to the manner in which an anthelmintic acts on a parasite. In a similar fashion inanimate causes of disease, even after penetration into the tissues, may be directly attacked by antidotal agents. Thus, hydrocyanic acid and various cyanide compounds may be transformed into non-toxic substances by sodium hyposulphite, even after they have been absorbed into the circulation. As these antidotes have already been discussed elsewhere, they will not be considered in this section, but, of the inanimate causes of disease, only the toxins, which stand in the very closest relationship to living pathogenic agents, will be dealt with in connection with antitoxin therapy.

GENERAL ANTISEPTICS

In high dilutions antiseptics do not kill bacteria but only inhibit their growth and multiplication, while in somewhat greater concentration they kill the adult forms but not the spores, these being destroyed only by strong solutions of the most powerful antiseptics.

Methods of Investigation.—In order to determine the power of a substance to inhibit bacterial development,—*i.e.*, its antiseptic power,—it is added to the

fluid culture-medium in varying amounts, and the lowest concentration is determined which prevents the growth of the bacteria or the development of the spores. In investigating the disinfectant value—that is to say, the bactericidal power—of a substance, silk threads, pieces of glass, beads, and the like are covered with bacteria or spores, in so far as it is possible in equal numbers, and these test objects are left for different periods of time in the disinfectant solution, which is kept at a fixed temperature. After the disinfectant has acted upon these objects, the bacteria must be, as far as possible, freed from it, in order that a portion of the disinfectant may not be carried over into the fresh culture-medium, for, as even very small amounts of disinfectants are sufficient to inhibit bacterial growth, this might lead to the false conclusion that the bacteria had been killed. Thus, for example, following a suggestion of *Geppert*, who was the first to call attention to this source of error, mercurial compounds are rendered harmless by precipitating them with ammonium sulphide. For further details concerning the method of determining disinfecting powers the reader is referred to text-books on bacteriology.

As in all living cells, in the bacterial cell also the carrier of vital functions is a mixture of colloids in a state of "Quellung" or hydration, principally proteids and lipoids, which latter are for the most part substances of as yet unknown constitution but which resemble the fats in their solubilities. In this mixture of a certain definite structure, the protoplasm, the ferment actions and the vital functions of the cells, such as assimilation, growth, and reproduction, take place in an aqueous solution of salts, the concentration of which is definite for each organism but varying within certain limits with the varying species of bacteria. A change of the salt content of the medium may inhibit the vital activity of the bacteria, and may, with them as with other plant cells, cause plasmolysis (*A. Fischer*), while drying renders the life of the bacteria latent, but destroys it only after very complete removal of all water or when the drying has lasted for a very long time.

Every alteration in the chemical composition of the protoplasm causes an injury to the bacterial cells. An example of the delicacy with which these cells react to alterations in the chemical composition of the medium in which they are placed, is furnished by the anaërobic micro-organisms, whose life is so dependent on a very low oxygen tension that an increase in the amount of oxygen in the surrounding medium is fatal or harmful to them.

Most especially an alteration or change affecting the colloids or lipoids results in damage to the protoplasm, and consequently every foreign substance must act as a poison to bacteria if it is able to penetrate into their interior and enter into a chemical or physicochemical reaction with their vitally important constituents. Inasmuch as these constituents of the protoplasm of all animal and vegetable cells are similar, and as the bacterial cells in respect to their permeability do not differ essentially from other cells, it follows that all general cytotoxins are also general poisons for bacteria.

While in all its detail it is not known on which of these reactions the bactericidal power of the general antiseptics depends, the disinfecting power of the salts of the heavy metals, of acids, and strong alkalies is attributed to their power of producing changes in the proteid

constituents of the bacteria, for their bactericidal power runs parallel with their power of reacting with proteids. In connection with the absorption of poisonous substances which possess affinities for the lipoids, their toxic action may be attributed to a disturbance of the relationship between the lipoids and the other constituents of the bacterial cells. Similarly the alteration of the protoplasm by powerful oxidizing agents, which also act as antiseptics, is readily understood. On the other hand, however, prussic acid poisons the cells by inhibiting oxidation, probably by inhibiting the oxidases. It is thus seen that the bacterial cells may be affected in many quite different fashions.

Inasmuch as the disinfectants are also general cell poisons, the most that may be expected is quantitative differences between the susceptibility of the bacteria and that of animal cells. These may in the first place rest upon **differences in permeability.**

The outer layer of the protoplasm, or the plasma skin, which in vegetable cells lies on the inner side of the cell membrane, behaves in many bacteria in a manner not essentially different from its behavior in other animal and vegetable cells, being readily permeated by water and by many substances which are soluble in lipoids but permeated with difficulty by salts. Such bacterial cells consequently readily undergo plasmolysis. In other varieties, however, this outer layer is readily permeable for salts also. Consequently the protoplasm of bacteria is, generally speaking, no better protected from an elective absorption by its outer layer than is the case with other cells.

The behavior of the external cell membrane is of more importance. In other vegetable cells this cellulose covering is readily permeable for all substances, and consequently, under the influence of substances with little power of permeation, the differences in osmotic pressure, which lead to plasmolysis, occur only on both sides of the external layer of the protoplasm. The bacterial cell membrane, however, does not consist, as in other vegetable cells, of pure cellulose but also contains nitrogen, and consequently its permeability is not to be taken for granted as being the same as that of other vegetable cells. On the contrary, it forms a barrier which opposes a resistance to the entrance into the cell of various substances. This may be observed in connection with the action of poisons which after passing through the cellulose membrane produce alterations in the constituents of the plasma skin. Thus, for example, other vegetable cells are so rapidly killed by $^1/_5$ normal (molecular) NaCl solution which is saturated with iodine that plasmolysis does not occur, for the iodine enters immediately into a chemical reaction with the surface layer of the protoplasm and abolishes its semipermeability for the sodium chloride. On the other hand, one may produce plasmolysis of bacteria with this very same solution (*A. Fischer*), for in them the iodine penetrates more slowly through the external membrane of the bacteria. Solutions of various metallic salts behave in a similar fashion.

The membranes surrounding the spores protect the internal contents of the cell much more effectively than does the external membrane of the bacteria, and it has been found that neither concentrated sodium chloride solution nor distilled water nor concentrated alcohol inflicts any damage upon spores, and that water, even after months, penetrates into them with great difficulty. It is probable, therefore,

that the astonishing resistance of spores to the actions of certain antiseptics is to be attributed to their slight permeability. Thus, for example, spores in general are particularly resistant to the toxic action of phenol and other lipoid soluble disinfectants which readily penetrate into the interior of adult bacteria. For instance, anthrax spores are killed by 4 per cent. carbolic acid only when exposed to it for days, while the adult bacilli are killed in 2–10 minutes by a 1 per cent. solution. Spores are also far more resistant to corrosive sublimate, 0.1 per cent. $HgCl_2$ killing anthrax bacilli in 10 minutes but the spores only after two hours. This tough skin of the spores may consequently be considered as a protective organ comparable to the shells which cover most vegetable seeds.

In addition to differences in the permeability of bacterial cells, differences in their susceptibility to various antiseptics is due in part to their **varying power of retaining and storing up the penetrating substances** in their protoplasm. When foreign substances pass through the outer membrane, as a general thing they continue to diffuse throughout the protoplasm until an equilibrium has been established on both sides of the outer layer, but, if the foreign substance undergoes a chemical change after absorption into the interior of the cell, such an equilibrium cannot be established. Under such conditions bacterial cells may absorb considerable amounts of substances, even from very dilute solutions, and hold them fast in the form of new compounds. Thus, marine algæ store up iodine in a form which is non-toxic to them, and certain plants are similarly able to absorb from soil containing considerable quantities of zinc as much as 13 per cent. of their weight in zinc salts (*Czapek*). In other cases, however, the new compound may be poisonous for the cell, so that a gradual poisoning results from its accumulation. The best-known example of such phenomena is the oligodynamic action of solutions of metallic salts first observed by *Nägeli* in algæ.

In *Bokorny's* experiments, only water distilled from glass into glass was non-toxic for the algæ, while if the water had come into contact with copper, silver, lead, etc., it was found to be toxic to these organisms, although it was impossible by chemical reagents to recognize the presence of metallic compounds in this water, so great was the dilution. That the toxic action under these conditions was due to a gradual accumulation of the metal in the cells of the algæ, resulting from the absorption of the metal from the infinitely dilute solution, is evidenced by the fact that by first bringing large quantities of algæ into these solutions they could be rendered non-toxic for others introduced later.

Lipoid Solubility of Antiseptics of Decisive Importance.—The solubility of the antiseptics in the outer layer of the protoplasm is the chief deciding factor for the rapidity with which they penetrate into the body of the bacteria. The power possessed by this membrane of dissolving many substances closely resembles the same power of fats, and, consequently, in general all substances which dissolve readily in fats are passively absorbed into the interior of these cells.

When foreign substances penetrate into the cells from the tissue fluids of the body,—that is to say, from an aqueous medium,—their absorption will depend on the partition coefficient resulting from their solubility on the one side in water and on the other side in fat-like solvents. In accordance with this law, first promulgated by *Overton,* lipoid soluble substances must necessarily be readily and rapidly absorbed by bacteria. This fact gives to a group of organic antiseptics, the phenols, cresols, alcohol, etc., certain advantages over the inorganic ones, of which only a few, such as corrosive sublimate, iodine, and osmic acid, are soluble in lipoids.

On the other hand, most of the salts, as well as the alkalies and inorganic acids, in short most solutions of strong electrolytes, are hardly at all soluble in fats, and consequently they are not absorbed through the unaltered plasma membrane. It is only when, by virtue of their power of precipitating or dissolving proteid, they destroy the external layers of the bacteria, that they are able to penetrate into the interior of these cells.

From these points of view a division of the general antiseptics into two groups may be made,—those which are soluble in the lipoids and which consequently are absorbed into the superficial layers of the bacteria, which contain more or less lipoids, forming one group, while the second group consists of those which are insoluble in the lipoids but which, by attacking the proteid constituents of the bacterial cells, are able to penetrate into them. Such disinfectants as are soluble in the lipoids and at the same time precipitate proteids belong to both groups.

The different manner in which the absorption of antiseptics of these two groups occurs is of more or less practical importance. The disinfecting power of the lipoid soluble antiseptics is determined largely by their partition coefficient between the cells and the surrounding media, and this is the reason why, when applied in oily solution, carbolic acid has no disinfecting power (*Koch*), for, on account of its great solubility in oil, it is held fast therein and does not penetrate into the bacterial cells. Further, carbolic acid penetrates the bacteria with more difficulty from media containing much proteid than it does from pure water, for here its chemical affinity to proteid more or less neutralizes its tendency to enter into solution with the lipoids of the bacterial bodies.

The disinfectants of the second group form compounds with the proteids, which are more stable than the loose physicochemical combinations formed by carbolic acid and proteid, and consequently the disinfecting power of metallic salts is even more impaired by a medium containing much proteid than is the case with phenol.

Influence of Dissociability.—That the reactions of the salts of the heavy metals, the acids, and the alkalies with the proteids of the bacteria are ion reactions is evidenced by the fact that the disinfec-

tant power of such metallic salts as those of mercury is not dependent solely, as was formerly believed, on the amount of soluble mercury contained in their solutions, but runs parallel with the degree of dissociation of these solutions,—*i.e.*, is determined by the concentration of the free mercury ions. If the total concentration of mercury were the decisive factor, it would necessarily follow that equimolecular solutions of different mercuric salts would exert equally powerful disinfectant actions, but, as a matter of fact, a comparison in the toxicity of mercury salts, which are dissociable in different degrees, clearly evidences the relationship between their toxicity and their dissociation (*Paul u. Krönig, Spiro u. Scheurlen*). Thus, according to *Höber*, the degree of dissociation and the disinfectant power of the three mercuric salts, the chloride, the bromide, and the cyanide, decrease in the same order (see table). The same thing may be shown for the behavior of other metallic salts,—for example, for the salts of silver and gold.

Disinfecting Action on Anthrax Spores

Concentration of solution.	Number of colonies developing— After 20 min.	After 85 min.
$HgCl_2$ 1 Mol.: 64 *l*	7	0
$HgBr_2$ 1 Mol.: 64 *l*	34	0
$HgCy_2$ 1 Mol.: 16 *l*	∞	33

There is, however, a remarkable exception from this parallelism between disinfecting power and dissociability of solutions of the salts of mercury, for a comparison of the disinfecting power and dissociability of solutions of mercuric chloride with those of mercuric nitrate, sulphate, and acetate, solutions of which are much more highly dissociated, shows that the mercuric chloride is much the strongest disinfectant.

Disinfecting Action on Anthrax Spores

Concentration of solution.	Number of colonies developing— After 6 min.	After 30 min.
1 Mol.: 16 *l* $HgCl_2$	43	0
1 Mol.: 16 *l* $Hg(NO_3)_2 + HNO_3$	2000	560
1 Mol.: 16 *l* $HgSO_4 + 4H_2SO_4$	1800	592
1 Mol.: 16 *l* $Hg(C_2H_3O_2) + C_2H_4O_2$	2737	1294

This exceptional behavior of corrosive sublimate is to be attributed to its solubility in lipoids, a property not possessed by those other more highly dissociated salts. As a result of this property, mercuric chloride penetrates into the bacteria more rapidly than other salts, and consequently its disinfectant action occurs more promptly. However, in case of a more protracted action, such as is of importance in connection with inhibition by dilute solutions of the development of spores, the differences in the disinfecting or (more correctly speaking) the antiseptic power of the different salts disappear.

The toxicity for tissue cells of the less highly dissociated quicksilver compounds is also relatively slighter, and consequently certain complex compounds of the metallic salts act much more mildly in the body. *Dreser* has shown that

solutions of the double salt, potassium and mercury thiosulphate, require a much longer time for the development of their toxic actions on yeast-cells, frogs, and fish than do solutions of other salts of mercury, which contain the same total quantity of mercury in a more highly ionizable form. Potassium and mercury thiosulphate is a complex salt which may be looked upon as being the potassium salt of a mercuric-sulphurous acid, which in aqueous solution is dissociated into potassium ions and $Hg(S_2O_3)_2$ ions. It is only as a result of the so-called secondary dissociation of the complex mercurial ions that simple mercury ions are set free. Thus is explained the lack of toxicity of this double salt for cold-blooded animals, although for warm-blooded animals it is almost as toxic as the ionizable mercury compounds, for in the body of the warm-blooded animal the compound ion is rapidly decomposed and simple mercury ions are set free. In the same way other organic metal compounds lack both the chemical reactions of the metal ions and their physiological actions, if the metal is dissociated not as a free metallic ion but as a portion of a complex one. Thus, potassium ferrocyanide neither gives the chemical reaction of iron directly nor does it exert its physiological effects, for it is dissociated into potassium ions and ferrocyanide ions.

Just as with the salts of the heavy metals, the disinfectant action of the acids is determined chiefly by their dissociability, for the disinfecting power of their solutions in general runs parallel with the concentration of hydrogen ions on which their toxic action depends. The highly dissociable inorganic acids, such as hydrochloric, hydrobromic, and sulphuric acids, are powerfully disinfectant, while phosphoric acid is much less so. The organic ones, such as acetic, formic, and boric acids, are, however, far more strongly disinfectant than would be expected from the degree in which they are dissociated. As was demonstrated by *Overton,* the undissociated molecules of these ether-soluble acids are soluble in the lipoids, and consequently penetrate into the bacteria more readily than the inorganic acids which are not soluble in these lipoids.

In an entirely similar fashion a comparison of the disinfecting power of potassium and sodium hydroxide and of ammonia, as also of the hydroxides of lithium, calcium, strontium, and barium, shows that in general the value of the alkalies for disinfection depends on the percentage of free hydroxyl ions in their solutions. However, here again the lipoid soluble ammonium hydroxide is an exception, possessing, in spite of its slighter dissociability, more powerful disinfectant action than corresponds to the concentration of the hydroxyl ions in its solutions.

Phenol is but slightly ionized in solution, but this is of slight significance, for its antiseptic action is not due to the ion C_6H_5O, but to the undivided molecules. This essential difference explains the opposite influence exerted by the addition of salts on the disinfecting power of solutions of salts of the heavy metals and those of carbolic acid, for it is possible to decrease the degree of dissociation of electrolytes by adding to their dilute solutions (in which dissociation is almost complete) another electrolyte possessing a common ion. Thus, a portion of the free mercury ions in solutions of $HgCl_2$ may be forced back into molecular combination by the addition of NaCl, and in this way both the degree of dissociation and the disinfecting power of the solution may be diminished.

Disinfection Experiments with Anthrax Spores.

$HgCl_2$	Concentration	Colonies developing after 6 min. expos.
$HgCl_2$	1 Mol.: 16 *l*	8
$HgCl_2$ + NaCl	1 Mol.: 16 *l*	32
$HgCl_2$ + 2NaCl	1 Mol.: 16 *l*	124
$HgCl_2$ + 4NaCl	1 Mol.: 16 *l*	382
$HgCl_2$ + 10NaCl	1 Mol.: 16 *l*	1087

(After *Paul u. Krönig*)

The disinfecting powers of solutions of carbolic acid are altered in an opposite direction by the addition of salt (*Scheurlen*), for, in the case of carbolic acid, the cresols, etc., the addition of salt markedly increases the disinfecting power of their solutions, this effect being produced not only by sodium chloride but by all salts. The augmentation of the disinfectant action runs parallel with the "salting out" power of the salts, for by this action the solubility of the carbolic acid in the water is diminished, and thus the partition coefficient between the medium and the cells is altered, so that the phenol penetrates into the bacteria in larger amounts than before (*Spiro u. Bruns*).

Disinfection Experiments with Anthrax Bacilli

Solution	Number of colonies after— 1 day	3 days	5 days
1% phenol	1520	1950	1650
1% phenol + 24% NaCl	96	0	0
2% phenol + 20% NaCl	1560	120	0
3% phenol	1200	1120	1010
3% phenol + 12% NaCl	0	0	0

Influence of Surrounding Media.—From the above it may be concluded that the action of the antiseptics on bacteria is due to their chemical and physicochemical affinity to various constituents of the bacterial bodies. If these affinities find similar opportunities for chemical or physical combination with substances present in the complicated organic culture-medium, there results a rivalry between those constituents of the bacteria and those of the culture-medium which are capable of reacting with the disinfectants. Consequently it is clear that the efficiency of the antiseptics will depend not alone on their concentration and the duration of their action, but also on the chemical composition of the medium in which they act. Their full power can be exerted only in aqueous solutions, and their action is much weaker in culture-media which contain considerable amounts of organic substances, particularly proteids. Herein lies the almost insurmountable difficulty which opposes a disinfection in the living body.

Behring, for one, has shown that a twofold to fourfold higher concentration of corrosive sublimate is needed to kill spores in blood-serum than to do the same in distilled water. Anthrax bacilli in aqueous media are killed even by 1–500,000 $HgCl_2$, but in bouillon only by a concentration of 1–40,000, while in blood-serum with the same length of exposure even 1–2000 is no longer efficient.

The influence of the medium expresses itself in different fashions according to the mechanism by which the antiseptic action is produced. It is particularly the proteid substances present in the secretions of wounds and in the tissue cells which divert the metallic ions away from the bacteria, and, as the albuminates form stable compounds with the salts of the metals, the antiseptic power of such solutions is permanently diminished in proportion to the amounts of the metals which combine with them. It is for the same reasons that iodine, which in a culture-medium containing but little proteid exerts a powerful disinfecting action, does so but feebly in the presence of much proteid. On the other hand, the antiseptic action of the ethereal oils which do not combine with proteids is much less impaired by them.

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CONSIDERATION OF THE INDIVIDUAL ANTISEPTICS

It will be sufficient for our purpose merely to name the more important antiseptics, and to discuss the actions of certain typical representatives of the different groups. The choice of an antiseptic will depend on the purpose for which it is to be used, certain of them being employed for the destruction of micro-organisms outside of the body, while others are used for the purpose of preventing their development in wounds and on mucous membranes.

Chlorine is the most powerful and energetic disinfectant which we possess, but it also exerts a destructive action on all organic material. It is a yellowish-green gas, with a suffocating odor and very irritant to the mucous membranes, which, in the presence of moisture, is an extremely efficient disinfectant, most bacteria and their spores being killed by concentration of 3 per cent. of chlorine gas in the atmosphere. Bromine acts less energetically, and iodine still more weakly (*Geppert, Paul u. Krönig*).

The employment of chlorine for the disinfection of various objects, living-rooms, etc., is very much limited by its destructive effect. Where, however, this is of no importance, as in the disinfection of

fæces, etc., one frequently uses chlorinated lime, a mixture of calcium hypochlorite, calcium chloride, and lime, which when treated with acids—on addition of HCl—gives off free chlorine. A freshly prepared solution of potassium permanganate on the addition of 0.9 per cent. HCl also gives off free chlorine, which may be used for the disinfection of the hands (*Paul u. Krönig*).

Chlorine water, Liquor chlori compositus, a yellowish-green, very irritating fluid, with a suffocating odor, containing 0.4 per cent. chlorine, is used as a corrosive and disinfectant in wounds and on mucous membranes, and was formerly employed as an intestinal disinfectant.

In the presence of water, chlorine oxidizes all organic material, for, by virtue of its strong affinity to hydrogen, it liberates nascent oxygen from the water.

Even very small amounts of chlorine gas irritate the mucous membranes of the eye and nose, and, if somewhat larger amounts are present in the atmosphere, they cause the well-known protective reflexes, dyspnœa and coughing. When stronger concentrations are inhaled, they may cause bronchitis and pneumonia. When chlorine is present in the air, its irritating effects may be diminished by sprinkling ammonia about so as to form the now volatile ammonium chloride.

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Sulphurous acid, H_2SO_3, whose gaseous anhydride, sulphur dioxide, SO_2, is formed by the combustion of sulphur, is at present hardly used at all for the purpose of disinfecting residences. [Sulphurous acid is the best—and in fact the only practical—means of killing the yellow-fever carrier, stegomyia fasciata, and in spite of its disadvantages it is used for this purpose, even in living-rooms. When thus employed all metallic objects and readily injured fabrics should, if possible, be removed from the room.—Tr.] It is a powerful reducing agent, and, by virtue of this property, is an efficient means of preventing fermentation, and is used for this purpose in the preparation of wine casks. It is a particularly powerful poison for moulds.

Quicklime, CaO, is used as an inexpensive means of disinfecting large quantities of material, such as privy vaults or the stools of typhoid patients, etc. It acts as a bactericide by virtue of its dehydrating power, and, after its transformation by the water into slaked lime, calcium hydrate, Ca(OH), as a powerful alkali destroys the bacteria. Finely powdered calcium hydrate suspended in water in a concentration of 20 per cent. is known as milk of lime, and its clear solution, containing about 0.17 per cent. of calcium hydroxide, is known as lime water.

Crude mineral acids are adapted for disinfection *en masse.*

Crude sulphate of iron acts chiefly as a deodorizer by virtue of its power of combining with sulphuretted hydrogen and ammonium sulphide.

Formaldehyde is an extremely valuable disinfectant for inanimate objects. It is a colorless gas which is very irritant to the conjunctiva and nasal mucosa, and when dissolved in water is a very powerful antiseptic and also a sufficiently powerful bactericide. Anthrax bacilli are killed in one hour by a dilution of 1 to 2000 and their spores by 1 to 1000. This drug readily penetrates into the bacterial bodies, and reacts with numerous organic substances and in particular coagulates proteid. It is very irritant to animal tissues, but after absorption is relatively non-toxic to the central nervous system, as it is almost completely decomposed in the body, only a small portion being excreted as formic acid. Another small portion is probably excreted in unaltered form, as after ingestion of formaldehyde the urine is weakly antiseptic. Used externally formaldehyde hardens or tans the skin, and consequently sweat secretion may be diminished by bathing the skin with its solutions. Formaline or formol is a 40 per cent. (by volume) aqueous solution of formaldehyde.

In ½ to 1 per cent. aqueous solutions formaldehyde is used for the disinfection of mucous membranes, but it is chiefly employed for the disinfection of residences, etc. Generated with steam and introduced into hermetically closed rooms, formaldehyde produces a reliable surface disinfection, for in gaseous form it reaches the surfaces of all the objects which are to be disinfected, and is deposited on them dissolved in extremely small drops of water. However, this method of disinfection does not exert any considerable disinfection except on the surface of the various objects. When the rooms are opened again the suffocating and irritating formaldehyde vapor and odor may be removed by the use of ammonia vapor, which combines with formaldehyde forming the non-volatile hexamethylenamine.

In disinfection of the skin, either that of the hands of the operator or the skin of the field of operation, the greatest emphasis is at present laid upon an energetic mechanical cleansing, which should be followed by a chemical disinfection in order to lessen as far as possible the number of germs hidden in the pores and glandular canals of the skin. Although complete freedom from such germs cannot be obtained, alcohol and corrosive sublimate have been shown by bacteriological investigation of disinfection of the hands to be the best substances for this purpose (*Paul u. Sarwey*). Even in a concentration of 5 per 10 per cent. ethyl alcohol inhibits the development of bacteria, but its disinfecting power increases with its concentration only up to a certain fixed point, and absolute alcohol exerts very slight disinfecting actions. In the strength of 50 per cent.

it occupies a position midway between 1–1000 corrosive sublimate and 3 per cent. carbolic acid.

In the disinfection of the hands, in addition to its bactericidal power, alcohol's property of dissolving the fatty skin secretions is of considerable importance, as is its power of penetrating the skin, by virtue of which property it is able to attack the bacteria in the deeper layers of the skin and to open the path for other disinfectants which may be used later (*Fürbringer, Ahlfeld, Mikulicz*).

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The disinfection of instruments and other objects, particularly those which may come in contact with wounds, may be accomplished by the use of 3 to 4 per cent. carbolic acid solutions, by lysol, and by other aromatic antiseptics, as also by 1 to 1000 sublimate solutions, which latter should not be used on metal instruments as they form amalgams with the metals. The same substances in weaker concentrations are also used in wounds as antiseptics.

In the disinfection of mucous membranes and wounds the use of higher concentrations of the stronger disinfectants is contraindicated, by the unavoidable damage to the tissues produced by these general cell poisons and by the danger of systemic poisoning from their absorption. While the antiseptics cause actual destruction of the tissue only in concentrations considerably stronger than those which prevent the development of bacteria, these drugs are all general cell poisons, and, even in very weak solutions, impair the vital functions of the tissues and thus interfere with their natural protective reactions and consequently prepare a favorable culture-medium for bacteria.

It is for this reason that the modern surgeon has given his preference to aseptic measures and has correctly abandoned the employment of antiseptics in the treatment of wounds. Even for the purpose of cleansing already infected wounds, the methods formerly commonly employed in the attempt to secure energetic disinfection have been abandoned, and to-day, in place of 1–1000 bichloride or 3 per cent. phenol or lysol solutions, much weaker solutions or milder antiseptics, like hydrogen peroxide, aluminum acetate, or boric acid, are employed for the purpose of cleansing wounds of their germs. These weaker concentrations are scarcely able to inhibit the development of bacteria, and perhaps in the treatment of wounds play only the rôle of sterile cleansing fluids.

Moreover, in view of the rapidity with which bacteria multiply, it would not be possible to obtain a radical purification of wounds even by the use of the stronger concentrations (*Schimmelbusch*), and

the damage done to the tissue cells by such procedures would endanger the healing of wounds, which, as a rule, are able by themselves to destroy the invading bacteria. A destruction of bacteria within the tissues of the human body by general—that is, by nonspecific—disinfectants is possible only in those cases in which one is willing to accomplish this at the cost of the sacrifice of tissue cells which are capable of regeneration, and consequently is of slight value. Examples of this would be the application of the tincture of iodine to the skin for the purpose of making an incision through tissues which are certainly free of bacteria, or the treatment of diphtheria by the local application of caustics for the purpose of killing the bacilli at the same time with the tissues.

The employment of antiseptics in wounds and mucous membranes, as has already been mentioned, is still further limited by the danger of systemic poisoning as a result of their absorption. This may be prevented if the distoxication of the antiseptic—by its elimination or chemical transformation—keeps pace with its absorption and thus prevents the attainment in the blood of a toxic threshold value. Theoretically this indication is best met by hydrogen peroxide, which, as soon as it comes in contact with the tissues, is decomposed into water and oxygen. Unfortunately, at the same time its local disinfecting power is diminished.

Formaldehyde and potassium permanganate also cause only local damage to the tissues and no harmful systemic effects. Unfortunately, the most reliable antiseptics, bichloride, carbolic acid, etc., owing to their lipoid solubility are readily absorbed. Perhaps it would be worth while to try and see if, like cocaine, they could be retained longer at the point of application by the addition of epinephrin to their solutions, and if the absorption of sufficiently concentrated solutions could be thus retarded.

As a rule, when toxic quantities of the general cell poisons are absorbed, it is the central nervous system which is most affected, and after it the organs of elimination, as during their elimination these poisons accumulate in these cells in somewhat high concentrations.

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Boric acid, H_3BO_3, is soluble in 20 parts of water at ordinary temperatures. Solutions of 1 to 3 in 100 are simply antiseptic and not bactericidal. As this weakly dissociated acid produces hardly any corrosive effect, it does not damage the tissues, and may be applied to surfaces of wounds and even such mucous membranes as the conjunctiva, or be used to wash out the stomach, the bladder, the uterus, etc. However, it must not be forgotten that boric acid is by no means lacking in toxicity, for in larger doses it causes gastro-

intestinal irritation, and, when considerable amounts of its solutions have been left in body cavities, it has in a number of cases caused fatal poisoning.

Borax, biborate of soda, $Na_2B_4O_7 + 10H_2O$, by virtue of its weak elective reaction, acts somewhat antiseptically, and is particularly effective against moulds and yeast-fungi, and is consequently used in the treatment of thrush.

Boric Acid and Borax as Preservatives for Food.—As a consequence of their relative lack of toxicity, boric acid and borax have been widely used as preservatives for meats, sausages, preserves, and so forth. Borax is also, though improperly, used as a preservative for milk, in which it, like all alkaline salts, impairs the coagulability of casein. The presence of either of these substances in food is not betrayed either by taste or smell, but in order to be effective they must be added in amounts ranging from 5 to 30 parts in the thousand. Consequently, as they are so generally employed for the preservation of our most important food-stuffs, it is possible that as much as several grammes may be ingested daily, and such doses when taken continually are by no means harmless, particularly inasmuch as boric acid is slowly excreted, and consequently can accumulate in considerable amounts in the organism.

According to the investigations of *Rost, Rubner,* and others, even daily doses of 0.5 to 1.0 gm. of boric acid exert a deleterious effect upon the utilization of the food, and augment the combustion of nutrient material, particularly that of non-nitrogenous substances, such as fat. Even in healthy individuals considerable loss of weight results after 5–12 days from the administration of 0.3 gm. daily, and in nephritic patients, in whom its excretion is retarded, the harmful results may be even more serious. These facts entirely justify the prohibition of its use as a preservative for food.

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The sulphites also, particularly sodium sulphite, are much used as preservatives for meat in amounts which often reach to 4 to 20 parts per 1000. Although large doses of sulphites can produce general harmful effects (*Pfeiffer, Rost*), in view of the rapid and almost complete transformation of the sulphites into the harmless sulphates (*Franz u. Sonntag*), it is still an open question whether the amounts necessary for the preservation of food-stuffs are sufficient to cause harmful effects.

[Even *Wiley's* own figures obtained in his experiments with the famous "poison squad," when carefully examined, fail to support his claim that the sulphites, in moderate amounts, are deleterious.—Tr.]

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Hydrogen Peroxide.—Oxidizing agents, by liberating nascent oxygen, act as disinfectants in a fashion fundamentally similar to chlorine. Hydrogen peroxide, which is decomposed with extreme readiness into water and oxygen, is the most powerful of these agents which may be employed in medicine. In aqueous solution it is decomposed with a very active liberation of oxygen by catalase, a ferment present in all cells, and also by many inorganic substances which in a state of very fine subdivision act like ferments.

This nascent oxygen acts as a disinfectant, but, as the action is limited to the short period during which the gas is generated, it can act only momentarily and superficially. This substance is suitable for use as a mouth-wash or gargle, or as a means of moistening dressings, for nascent oxygen destroys disagreeable-smelling and toxic decomposition products.

When injected into closed body cavities, such as the peritoneal cavity, hydrogen peroxide in unaltered form may enter the blood and cause sudden death as a result of the generation of gaseous oxygen in the blood.

Ferments, too, are rapidly destroyed by hydrogen peroxide. Its employment as a preservative for milk prevents souring, but at the same time destroys the enzymes and antitoxic substances normally present in milk.

Potassium permanganate, $KMnO_4$, also acts as an oxidizing agent, which is very readily reduced by proteid as well as by all other labile organic substances. The manganese oxide, which results from this reduction, forms a brown precipitate, causing brown spots on the skin and elsewhere. Even 1 per cent. solutions cause a caustic action on the surfaces of wounds and mucous membranes, but in a concentration of 1 to 1000 it deodorizes foul-smelling putrefaction products and exerts a weak disinfectant action. It may consequently be used for the washing of wounds and mucous membranes or as a mouth-wash, etc.

In this connection, mention should be made of the employment of potassium permanganate as an antidote in poisoning by phosphorus, morphine, and other toxic substances, which are readily oxidized and rendered non-toxic, but benefit may be expected from its employment only if these poisons are still present in the stomach. Potassium cyanide also is transformed by it into the less toxic potassium cyanate.

Potassium chlorate, $KClO_3$, is weakly antiseptic by virtue of its oxidizing powers. When heated, it oxidizes so energetically that, when mixed with readily combustible substances, an explosion may result from such slight warming as is produced by their trituration in a mortar. In the body it gives off its oxygen very slowly and is in largest part (about 90 per cent.) excreted in the urine. Even in strong concentrations it hardly inhibits the growth of bacteria, and

consequently it is questionable whether, when used as a gargle, it acts better than solutions of indifferent salts. Formerly curative effects in diphtheria were attributed to its action after absorption, and even now it is administered in doses of 4 to 6 gm. per diem in pyelitis and cystitis, with the idea that it endows the urine with antiseptic properties. Its internal administration in doses of more than 8 gm. per diem [or in much smaller doses.—Tr.] is under all circumstances attended by great danger, and with impaired renal function even smaller doses are dangerous (*Quincke*).

After absorption potassium chlorate penetrates into the red blood-cells with relative ease and transforms the hæmoglobin into methæmoglobin, so that the blood acquires a brownish color and the spectroscope shows a characteristic narrow stripe in the red portion of the spectrum. When this action is produced in a sufficient degree, all the symptoms of methæmoglobinæmia result (see p. 451). In very acute cases internal asphyxia results and death occurs in a few hours. In somewhat more protracted cases hemorrhages, diarrhœa, vomiting of greenish-black material, and all the other results of the destruction of the red cells occur. Agglutination of the red cells occurs, causing thrombi, infarcts, and ecchymoses, and the broken-down cells are deposited in the organs which normally destroy them, while the liver and spleen become swollen and jaundice develops.

The urine acquires a reddish-brown to black color and contains proteid, broken-down red cells, methæmoglobin, and hæmatin, and, as a result of blocking of the renal tubules, anuria and death with uræmic symptoms result. Doses which exceed 10 gm. can cause severe poisoning, while 15 to 20 gm. are, as a rule, fatal. The treatment can consist only in stimulation of diuresis to accelerate the elimination of the poisons, but bleeding and saline infusions are also recommended.

As in various infectious diseases the red blood-corpuscles have to some extent become more permeable to various salts, the internal administration of potassium chlorate in these conditions is contraindicated, just as it is in nephritis. Moreover, the use of large quantities of potassium chlorate solutions as a gargle has often caused serious poisoning, particularly in children, as a result of the unavoidable swallowing of the drug.

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MERCURIAL SALTS

In vitro the soluble and dissociable mercury compounds are powerful disinfectants, but the proteids present in wound secretions very markedly lessen their disinfecting power. Corrosive sublimate, the bichloride of mercury, $HgCl_2$, which is soluble in 17 parts of cold water, and the other soluble mercuric salts damage the cells of the tissues even in those low concentrations which prevent the development of bacteria. Moreover, the employment of larger quantities of even dilute solutions of these salts is limited by the danger of their absorption, which is especially great when they are used for washing out large wounds or mucous membranes.

Bichloride of mercury with proteids forms albuminates which with an excess of proteid and sodium chloride form soluble double salts of mercury albuminate and NaCl. As a consequence, the coagulum at first formed by their local action soon goes into solution and is absorbed, and, as a result, numerous acute and subacute mercurial poisonings have occurred, particularly after the postpartum use of a bichloride solution as an intra-uterine douche.

For the purpose of preventing the formation of insoluble mercury albuminates, sodium chloride is added to bichloride solutions, many of the bichloride tablets containing this salt, although the disinfectant power is impaired by this addition. Recently, in place of the sublimate a compound of mercuric sulphate with ethylenediamine has been recommended under the name of sublamine, which, being a complex mercuric salt, does not precipitate proteid or cause irritation of the tissues.

Mercurial Poisoning.—When large quantities of mercury are rapidly absorbed, the systemic effects are exerted principally on the central nervous system and the organs of elimination, in this case chiefly the large intestine and the kidneys. As a result of the accumulation of relatively large amounts of mercury in the cells through which this metal is excreted, these cells undergo necrosis, and nephritis and colitis result, the latter causing abdominal pain, tenesmus, and diarrhœa containing blood and shreds of the mucous membranes. The toxic action on the central nervous system expresses itself in a condition of stupor or apathy and finally by collapse, as a result of which the patient dies with a subnormal temperature usually only after 5–10 days. Post mortem one finds hemorrhagic diphtheritic inflammation of the cæcum and colon and parenchymatous nephritis, often with calcium infarcts in the kidneys, as a result of the deposition of calcium phosphate and carbonate in the necrotic renal epithelium. When rapidly absorbed, 0.1 gm. of bichloride may produce fatal poisoning. The maximal dose of the soluble mercuric salts is 0.02 gm. per dose, 0.06 gm. per diem.

In less acute cases the first symptoms noted are those of the mercurial stomatitis, salivation, metallic taste, and disagreeable odor in the mouth, with redness and swelling of the gums and tongue. In such cases the symptoms due to intestinal and renal lesions appear only some days later. The accumulation of mercury in the body as a result of its long-continued administration and chronic mercury poisoning are described on pages 415 and 542.

Silver salts.—The dissociable and soluble silver salts are also very strongly antiseptic, preventing the development of many bacteria even in the blood-serum and in a dilution of 1 to 80,000. Silver lactate (actol) and silver citrate (itrol) are preferred by some surgeons to corrosive sublimate.

Silver nitrate in different concentrations is used for the disinfection of mucous membranes,—for example, in 2 per cent. solution as a means of preventing gonorrhœal ophthalmia in the new-born, and in 2–4 per cent. solutions in the treatment of urethral gonorrhœa.* However, when thus used its action is confined to the

* [The astringent and disinfectant actions of silver compounds do not account entirely for their almost specific effects in gonorrhœal inflammations. It is highly probable that they owe much of their curative action to their power of attracting the leucocytes to them,—*i.e.*, to their chemotacic powers.—Tr.]

surface of the mucous membranes, as silver combines with proteid and sodium chloride. As the organic silver compounds do not directly combine with proteid and NaCl, such compounds as *protargol,* a solution of an albuminate of silver, *argonin,* a compound of silver with casein, and *argentamine,* ethylenediamine silver phosphate, exert a more penetrating action.

In man systemic poisoning as a result of the absorption of silver does not occur, but after the long-continued use of silver compounds a peculiar grayish discoloration of the skin and of various internal organs results from the deposition in these tissues of insoluble metallic silver, a condition to which the name of argyria is given.

The essential action of the salts of **copper, zinc,** and **lead** is that of astringents and corrosives. **Aluminum acetate** exerts both astringent and antiseptic actions, and has once more come into use as a mild antiseptic in the treatment of wounds.

ANTISEPTICS BELONGING TO THE AROMATIC GROUP

Numerous aromatic substances which are sufficiently soluble in water to reach the cells, and sufficiently soluble in lipoids to penetrate them readily, possess antiseptic and disinfectant properties, but in stronger concentrations they kill the cells of the tissues and when absorbed are typical nerve poisons. Among these the most efficient are the various phenols and their ethers (*Laubenheimer*). As the aromatic hydrocarbons are less powerful than the phenols, benzol is a feebler antiseptic than carbolic acid, toluol than the creosols, naphthalin than the naphthols, etc. This is probably to be explained by their slighter solubility in water. The toxicity of the phenols does not increase with the number of hydroxyl groups, the bivalent phenols, brenzcatechin, hydroquinone, and resorcin, being less toxic than carbolic acid. The substitution of acid radicals for hydroxyl groups, as also the introduction of acid groups in any position in aromatic molecules, markedly lessens their activity. In spite of this, free aromatic acids, benzoic acid, salicylic acid, etc., are antiseptic and cytotoxic, but their neutral salts, which are insoluble in the lipoids and which consequently are unable to penetrate cells rapidly, are not.

Fate in the Body.—Inasmuch as in the organism the benzol ring, as a rule, remains intact, the fate of the aromatic substances in the organism differs from that of substances of the aliphatic series. In general, the aromatic compounds, after undergoing oxidation or losing some of their radicals, enter into synthetic combination with various intermediary metabolic products and form non-toxic substances. Thus, the phenols are conjugated in the liver with sulphuric and glycuronic acids, and many of the aromatic acids are combined in the kidney with glycocoll, the halogen substituted benzols, for example, combining with glycocoll and forming mercapturic acids.

Phenol, C_6H_5OH, or carbolic acid, is the type for the whole group. It occurs as colorless crystals, with a characteristic penetrating odor, which on exposure to air turns pink. It is soluble in 20

parts of water and is readily soluble in the lipoids, so that it readily penetrates into all tissues. In concentrations ranging from 1–200 to 1–30, it is a very efficient bactericide, killing most bacteria, but spores are extremely resistant to it. It was carbolic acid which was used by Lister when he introduced the antiseptic method into medicine, and in the antiseptic era it played a far more important rôle than at present, for it has in large part been replaced by similar antiseptics, but more particularly because to-day chemical disinfectants are employed only to a limited extent in the treatment of wounds.

Local Action.—Concentrated solutions of carbolic acid are powerfully corrosive, and when applied to the skin cause a white eschar, which later turns red and then brown, and which is finally cast off without the formation of pus. Even 5 per cent. solutions cause burning and pain and later local anæsthesia. More dilute solutions also can irritate the skin or on longer contact cause necrosis. Consequently, as carbolic acid readily penetrates the skin, dressings moistened with 2–3 per cent. carbolic acid, if left in place for a considerable time, may cause dry gangrene of the fingers and toes.

Toxicology.—This drug is rapidly absorbed wherever applied, even through the skin, and its systemic action is exerted chiefly on the central nervous system. In animals poisoned by it, at the start symptoms of excitation of the medullary and spinal centres preponderate, but in man, when poisonous amounts are absorbed, paralysis of the central nervous system occurs, usually without preceding convulsions. As even 1 to 2 gm. can produce poisoning and as 3 to 10 gm. are usually fatal, the maximal dose for internal administration should be 0.1 gm.

Poisoning with carbolic acid usually occurs as a result of suicidal attempts or of mistaking liquefied carbolic acid for more dilute solutions.* When concentrated solutions or the pure acid are swallowed, corrosion of the mucous membranes like that produced by concentrated mineral acids results, but in addition, because of the extreme rapidity with which absorption occurs, the local symptoms are quickly obscured by those of the systemic poisoning and very quickly, usually after a few minutes, the patient becomes completely unconscious and falls into a state of profound collapse.

When absorbed from the rectum or from the uterus, as may occur with its careless use post-partum, even relatively small amounts of carbolic acid may produce severe systemic poisoning, for in these cases the poison passes directly into the general circulation without first going through the liver. For the same reason, carbolic acid is distinctly more toxic when absorbed through the skin.

In former times, when carbolic acid was much more widely used in surgery, less acute carbolic acid poisoning was frequently ob-

* Carbolic acid liquefied by the addition of 10 per cent. of water.

served, beginning with vertigo, headache, a tipsy stupor, and vomiting, and in more serious cases frequently causing cold sweats, cyanosis, and small frequent pulse, with collapse and marked fall of the body temperature.

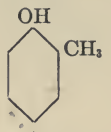
In such cases the process of distoxication proves inadequate, although ordinarily by the formation of conjugated sulphuric and glycuronic acids the organism can render even considerable amounts of carbolic acid harmless, provided they are gradually absorbed. As a portion of the carbolic acid is oxidized in the organism to dioxybenzols and is excreted in the urine chiefly in the form of hydroquinone-sulphuric acid, and as in the urine this substance is readily transformed into greenish-brown to black oxidation products, the urine, when carbolic acid has been absorbed in considerable amounts, gradually acquires a dark color on standing or is already discolored when passed. When too large amounts have been absorbed, both carbolic acid and the dioxybenzols are excreted without undergoing conjugation, and may cause albuminuria and nephritis.

Treatment of Carbolic Acid Poisoning.—When the poison has been taken by mouth, the most important indication is to wash out the stomach immediately, and, if this is done quickly enough, the corrosion caused by the poison—in contradistinction to that caused by concentrated acids, alkalies, etc.—may heal without leaving serious results. [A 15–20 per cent. solution of alcohol should, whenever possible, be used in washing out the stomach in these cases.—Tr.]

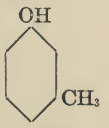
Saccharated lime has also been recommended as an antidote, as this forms an insoluble calcium carbolate. *Both animal experiments and clinical experience have demonstrated the futility of administering sodium sulphate with the idea of augmenting the synthesis of ethereal sulphuric acid and thus rendering the absorbed phenol non-toxic (Tauber, Marfori).*

Sulphocarbolates.—If carbolic acid be dissolved in concentrated sulphuric acid, sulphocarbolic acid is formed, which is far less active than carbolic acid itself. The iodized parasulphocarbolic acid has been introduced commercially under the name of sozoiodolic acid, and has been used in the form of its zinc salt in the treatment of gonorrhœa and in the form of its mercurial salt in the treatment of lues. However, in all probability these compounds possess no advantage over other zinc and mercury salts.

The Cresols.—Next to carbolic acid the cresols are the most important aromatic disinfectants. For a long time it has been the custom to use for disinfection on a large scale, in place of the expensive pure carbolic acid, the cheaper raw acid which remains after pure carbolic acid has been extracted from coal-tar. In addition to other products obtained from coal-tar by dry distillation, such as naphthaline, pyridine, etc., this raw carbolic acid contains three isomeric cresols, homologues of phenol, in which a methyl radical replaces a hydrogen atom in the ortho-, meta-, and para-positions.



Orthocresol



Metacresol

Paracresol

The powerful disinfectant action of these cresols was quickly recognized, but their insolubility rendered their utilization as disinfectants difficult. An impure mixture of these three isomers is known as crude cresol or tricresol, while **creolin** is an emulsion of cresols and hydrocarbons of uncertain and varying composition. In the form of solutions of their alkaline soaps, the cresols have been widely used, **lysol** and the **liquor cresolis compositus** being such solutions which contain about 50 per cent. of cresol. Many similar preparations may be obtained under different names. For gross disinfection quite extensive use has been made of saprol, which is a mixture of 80 parts of crude carbolic acid and 20 parts of petroleum, and which, because of the presence of the lighter hydrocarbons, floats on the materials to be disinfected and covers them over with a thin coating, from which the cresols, etc., gradually permeate the whole mixture.

Formerly it was thought that these cresols were less toxic than carbolic acid, but, as a matter of fact, when absorbed, they are by no means less toxic. Among themselves, however, they are not equally toxic, metacresol being the weakest, and paracresol for many species of animals almost twice as toxic, while orthocresol lies between (*Wandel, Tollens*). While the cresols are more powerfully antiseptic than phenol, it is practically of greater importance that, on account of their slighter absorbability, they are, in proportion to their disinfecting power, relatively less toxic.

When absorbed, the cresols produce the same toxic systemic effects as carbolic acid (*Kochmann*). Suicide by swallowing lysol has been particularly common in recent years, and causes the same unconsciousness and collapse as does carbolic acid, the only difference being that in these cases convulsions appear to occur more frequently than in carbolic acid poisoning. The treatment of such poisoning is the same as that of carbolic acid poisoning.

In cresol poisoning also, the urine becomes dark colored (*Matter*), and nephritis occurs. The cresols are excreted with the bile (*Wandel, Bial*), and may cause parenchymatous hepatitis.

Thymol.—Of the higher homologues of phenol, thymol, methylisopropylphenol, is a more powerful antiseptic than carbolic acid or the cresols. It is very insoluble in water—1 to 1000—and is consequently absorbed with difficulty, and may, therefore, be used as a relatively non-toxic antiseptic wash.

Of the dioxybenzols, **resorcin**, metadioxybenzol, is used in the treatment of diseases of the skin and as an antiseptic wash and has also been used internally.

Pyrogallol, or pyrogallic acid, trioxybenzol, is a powerful reducing agent which is used in the treatment of psoriasis and other parasitic diseases. It is very irritant or even corrosive and stains the skin black, and, as it is also readily absorbed, is a powerful poison to the blood, reducing oxyhæmoglobin to methæmoglobin.

In the treatment of skin diseases, use is also made of **chrysarobin, naphthaline,** and **beta-naphthol,** as also of the various tars obtained by the distillation of wood, such as **pix liquida,** which contains phenol and various other esters, and also terpenes and resinous acids, or the purified tar, **anthrasol.**

Ichthyol, a vile-smelling mixture containing 10 per cent. of sulphur, which is obtained by the distillation of bituminous rocks from the Tyrol containing fossil fishes, is used for similar purposes.

Balsam of Peru is an antiseptic agent which irritates the tissues but slightly. It occurs as a thick brown liquid, and is a mixture of 40–60 per cent. of the benzylester of cinnamic acid, 10 per cent. of free cinnamic acid, and various resins. Even this relatively non-toxic antiseptic, however, when absorbed in considerable quantities, like all the above-mentioned antiseptics, can and does cause damage to the kidneys.*

Finally, **salicylic acid** (ortho-oxybenzoic acid) is a powerful antiseptic, hardly exceeded in its activity by phenol, which, however, is almost insoluble in water. On the skin it exerts a keratolytic and antisudorific action, and on mucous membranes it is irritant or corrosive. Its salts are only feebly antiseptic and are not corrosive. For its employment as an internal disinfectant see page 530.

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Iodoform.—While the treatment of wounds by antiseptic solutions has constantly gone more and more out of fashion, iodoform is still widely used as an antiseptic dusting powder, although much less freely than formerly. Its value lies in the fact that it is very insoluble, and consequently, without causing damage to the tissues, remains as a harmless reserve store from which an actually effective substance or substances are gradually split off under the influence of the secretions of the wound. It occurs as a yellow crystalline powder, with a characteristic disagreeable and penetrating odor, and is almost insoluble in water, but readily soluble in fats and ether. It is much used in the treatment of purulent sinuses and ulcers, and with particularly good effect in tubercular conditions. In vitro it is very feebly bactericidal, even tubercle bacilli, like most other bacteria, being unaffected even when exposed for weeks to iodoform vapor. On the

* [A temporary albuminuria of considerable severity often follows the external application of balsam of peru in the treatment of scabies.—Tr.]

other hand, cholera vibriones are relatively quickly killed by it (*Baumgarten, Troje u. Panke*). On the surface of wounds it gradually goes into solution, and from this solution iodine is slowly and continually liberated, exerting an antiseptic and deodorizing action on the wound secretions. As iodine is chemically extremely active, it acts upon all the chemical labile organic substances present in the secretions of the wound, and in this fashion destroys putrefactive substances and probably also renders various toxins harmless * (*Behring*). This mild iodine action, resulting from its slow liberation, also acts as a mild stimulant for the formation of granulations in tubercular lesions, etc.

Toxicology of Iodoform.—The iodine liberated from iodoform is absorbed partly as an albuminate, or in the form of other organic compounds, and in part as iodides of the alkalies, and is excreted in the urine in part as inorganic iodides and in part in organic combinations of still unknown nature. Consequently, iodoform, like the alkaline iodides, may cause general iodine effects, such as coryza and acne (see p. 400). However, iodoform is also absorbed unchanged, for the acute iodoform poisoning, occurring when it is absorbed in too large amounts, differs very essentially from the toxic effects produced by inorganic iodine compounds. Such poisoning develops slowly, the first symptoms noted being those of vague disturbances of the central nervous system, which are followed, after several days, by conditions of mental excitement, hallucinations, and delirium, alternating with confusion and stupor, but in some cases the poisoning resembles a pure narcosis. These symptoms of poisoning are due to the absorption of iodoform in a form which is neurotropic, *Loeb* having been able to find iodine in the brain after the administration of iodoform and other lipoid soluble organic iodine compounds, although even after the administration of large quantities of organic iodides no iodine could be found there. When absorbed by the cells of the brain, iodoform acts as a narcotic in the same fashion as other lipoid soluble indifferent substances; but, as its absorption into, and particularly its elimination from, the brain occurs much more slowly than does that of the closely related chloroform, its action often lasts for days or weeks. In such cases, just as after chloroform, fatty degeneration of parenchymatous organs occurs.

The treatment for iodoform poisoning can consist only in its immediate removal from the situation from which it is being absorbed. However, owing to the firmness with which it is combined with the nerve-cells, the unfavorable course of the poisoning cannot always be prevented by such measures.

Iodoform Substitutes.—The extremely disagreeable odor of iodoform has led to the introduction of numerous substitutes, chiefly iodized aromatic com-

* According to *Heile*, under these conditions other soluble decomposition products containing iodine are formed, which produce an antiseptic effect.

pounds which are themselves antiseptic and which are also supposed to liberate iodine in the tissues, but none of these substitutes has proven equally efficient with iodoform. It appears that benzol derivatives, such as Loretin (iodoxyquinolinesulphonic acid), Nosophen (tetraiodophenolphthalein), Losophan (triiododimetacresol), Sozoiodol (iodoparaphenolsulphonic acid), etc., in which the iodine is combined directly with the benzol ring, do not liberate iodine in the organism and consequently act only as aromatic disinfectants. On the other hand, similar pyrrol derivatives, such as Iodol (tetraiodopyrrol), do liberate iodine, Recently Isoform (paraiodoanisol), has appeared to be of value. Of the benzol derivatives in which iodine is present in a side chain, Aristol (dithymoldiiodide) and Europhen (diisobutylorthocresoliodide) may be mentioned.

Bismuth preparations, such as Xeroform (tribromphenol-bismuth) and Airol (bismuth-oxyiodogallate), and formaldehyde compounds, are also employed for the same purpose as iodoform.

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URINARY ANTISEPTICS

The drugs which are excreted in the urine in an antiseptically active form are discussed in another section (see p. 367).

INTESTINAL DISINFECTION

Any real disinfection of the intestines is impossible of attainment, and in fact it is doubtful whether it is possible by pharmacological agents to cause even an inhibition of the growth of the intestinal flora. It must be remembered in this connection, however, that great difficulty attends the demonstration of any diminution of the growth or of the activity of intestinal bacteria (*Stern*).

Often the quantity of the conjugated aromatic substances of the urine which are formed by proteid decomposition in the intestine has been used as a measure of the amount of bacterial fermentation in the intestine; but, in addition to the fact that this factor permits an estimation only of the intensity of proteid putrefaction, and not of the activity of other bacteria,—for example, those fermenting carbohydrates,—the quantity of these aromatic substances excreted in the urine depends also upon the extent to which they are absorbed, as also on the extent to which they are further transformed in the organism. It is, therefore, clear that this method of estimating the bacterial activity in the intestine must be very unreliable. The attempt has also been made to determine the effects of supposed intestinal disinfectants by determining the number of bacteria in the fæces before and after the administration of such drugs, as also by determining the viability of non-pathogenic foreign bacteria after their passage through the intestine. These methods also permit conclusions only as to the life conditions for the bacteria in the lowest segments of the intestines, while the particularly important thing in intestinal disinfection is the influencing of bacteria in the small intestine. For these various reasons, those experiments in which the bacteria were counted in material obtained from the small intestine through fistulæ have given the most reliable information. [Even such investigations have indicated that few, or none, of the so-called intestinal antiseptics exert any appreciable effect on the intestinal flora. The composition of the diet appears to be one of the most important factors in determining the nature or types of the strains predominating in the intestine.—Tr.]

Only those substances can act as intestinal disinfectants which are not absorbed completely in the upper portion of the intestine

and which, on account of their difficult absorption, are relatively non-toxic. One of the most widely used intestinal antiseptics is salol, or phenyl salicylate, which is rather insoluble and is decomposed in the intestine into its two antiseptic components, phenol and salicylic acid. Salicylic acid itself, as also napthaline, beta napthol, and particularly thymol, have been stated to exert more or less disinfectant action in the intestine. The most efficient intestinal disinfectant, however, is calomel, which probably owes its efficiency more to its cathartic action than to the fact that it is partially transformed into soluble mercury compounds which possess antiseptic powers. [This is very doubtful. See *Harris.*—Tr.]

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ANTHELMINTICS

Anthelmintics, or vermifuges, are drugs used to expel intestinal animal parasites, such as the various tapeworms, Tænia solium, T. mediocanellata, Bothriocephalus latus, round worms or Ascaris lumbricoides, Oxyuris vermicularis, and the hook-worm, Ankylostoma duodenal or Uncinaria americana. They are all substances the value of which has been discovered empirically, and which possess the property of reaching the lower portion of the intestine without being absorbed to any great extent. Their toxic action is by no means specific, for, being absorbed with difficulty, they come in contact with the parasites in the intestines in much stronger concentrations than reach the tissue cells of the host when they are absorbed. If they are absorbed in large amounts, they are all toxic in the host also.

These anthelmintics do not always kill the parasites, but only benumb them, so that the worms are no longer able to hold fast to the mucous membrane by their suckers, and consequently may be readily evacuated with the general intestinal contents. For this reason, in case the vermifuge itself does not produce catharsis, a cathartic should be administered some time after the vermifuge, in order that both the parasites and the unabsorbed portion of the toxic drug may be expelled from the intestine.

As a preliminary preparation in the treatment, it is advantageous to empty the intestine by a mildly acting laxative in order that the action of the drug on the parasite will not be interfered with by the presence of too large amounts of material in the intestine. However, it is a mistake to empty the intestine completely by too long-continued preliminary fasting or purging, for this increases the danger of the absorption of the vermifuge and consequently augments the danger of poisoning.

Oleoresina asipidii, obtained from the rhizome of filix-mas, or male fern, is a dark green thick oil, with a very disagreeable taste,

which contains a number of active principles which have been isolated in pure form only comparatively recently (*Poulsson, Böhm*).

These are non-nitrogenous acids, of which the most important is filicic acid, or filicin, which in crystalline form is inactive but occurs in the fresh oleoresin in an amorphous active form.

Other active principles are flavaspidic acid, albaspidin, and aspidinol, etc., and also an amorphous substance named filmaron (*Kraft*). In other ferns very similar substances occur, which, like those named above, are all compounds of butyric or isobutyric acid with phloroglucin and its homologues.

These active principles are both neurotoxic and myotoxic poisons. In invertebrates *Straub* has found that filicic acid is very toxic to smooth muscle, and it is probable that the medicinal activity of male fern is dependent on its power of paralyzing the muscles of the different tænia.

In mammals filicic acid causes excitation of the central nervous system, evidenced by twitching of the muscles and often by tetanic convulsions, and finally it causes paralysis of the muscles, heart-failure, and collapse. In man also poisoning has often been observed after too large doses or improper administration of this drug. Under these conditions the first symptoms are due to gastro-intestinal irritation, which causes nausea, vomiting, and purging, later stupor and faintness or even convulsions may develop, while cardiac weakness, disturbances of respiration, and temporary impairment of the vision, or even permanent blindness due to optic atrophy, may also result from its administration. Most of the cases of poisoning recorded have been the result of exceeding the admissible dose (see below), which at the highest should not be larger than 8–10 gm. of the oleoresin, or have resulted from the repetition of an unsuccessful treatment on the following day. [Many American authors unite in recommending that the maximum dose should not exceed 6.0 gm.—Tr.]

In the usual doses, not exceeding 8.0 gm., male fern in almost all cases is well borne if administered on a not entirely empty stomach and if, one or two hours after its administration, calomel, senna, or other efficient cathartic be administered, so as to bring about a thorough removal of the drug. [Castor oil should not be used as a cathartic in these cases, for the literature shows that many of the cases of poisoning have been those in which this drug, which is a solvent for the poisonous active principles, has been administered.—Tr.] The relative non-toxicidity of filicic acid for the host is due in part to the destruction of this drug in the organism of the higher animals (*Straub*).

Kousso, or koosso, the dried female flowers of Hagenia abyssinica, long used as a tænicide, contains substances which, like the active constituents of the various ferns, are compounds of butyric acid with members of the phloroglucin series, the most important being the amorphous koussotoxin (*Lobbeck*). In the lower animals this too is a powerful muscle poison, resembling filicic acid. From 15.0 to 25.0 gm. of the crude drug in the form of a decoction acts as an efficient

vermifuge, usually without causing serious symptoms. However, only the fresh blossoms are reliable in their action.

Kamala, the glands and hairs of the capsules of Mallotus philippinensis or Rottlera tinctoria, occurs as a granular brick-red powder, odorless and nearly tasteless, and in the dosage of 6.0–12.0 gm. is employed as a mildly acting vermifuge. As this drug itself exerts a cathartic action, it need not be followed by a laxative. Its active constituent, the resinous rottlerin, is also a phloroglucin derivative.

Pelletierine.—The active constituents of granatum, the bark of Punica granatum, and of the betel or areca nut, are all alkaloids. Granatum contains, in addition to very considerable amounts of tannic acid, a number of alkaloids of which pelletierine and isopelletierine are very toxic to the various tapeworms. [The pelletierine of commerce is a mixture of various alkaloids.—Tr.] Doses of 0.3–0.4 gm. pelletierine sulphate or tannate usually act as efficient tænicides without causing severe symptoms of poisoning. They are best administered together with 0.5–1.0 gm. of tannic acid, in order that the alkaloid may be retained in the intestine in the form of its rather insoluble tannate. The symptoms of poisoning, when this occurs, consist of dizziness, faintness, and weakness, and occasionally serious disturbances of vision. The crude drug is of uncertain activity except when fresh, and, as from 50 to 60 gm. must be taken within an hour, the large amount of tannic acid contained in it (sometimes as much as 22 per cent.) is a great disadvantage in connection with its use, as it may cause nausea and vomiting. The tannin can, however, be removed from the decoction by treating it with chalk or milk of lime.

On the higher animals pelletierine is a central nervous excitant (*v. Schröder*) and, in addition, exerts an action on the muscles similar to that of veratrine. Its relatively great toxicity on tapeworms is probably dependent on this action on the muscles.

Betel or area nuts are used, particularly in veterinary practice, as tænicides. Arecolin, the alkaloid contained in them, belongs, according to its pharmacological actions, in the muscarine and pilocarpine group (see pp. 153 and 372). On account of the readiness with which it is absorbed, this drug is too dangerous to be used as a tænicide.

Santonin, the active principle of santonica, or levant wormseed, which is the only drug used to expel the round worm, Ascaris lumbricoides, is an acid anhydride. According to *v. Schröder,* santonin does not kill these worms, but only drives them down into the large intestine, from which they may be readily removed by a cathartic. It is absorbed with extreme difficulty, and is consequently to a large extent excreted in the fæces, but a certain portion may be absorbed and cause poisoning.

Pharmacologically it is a convulsant, which in animals causes epileptiform convulsions, marked depression of the temperature, and death. In man also its use has been observed to cause not only

nausea, vomiting, and purging, but also convulsions. It frequently, even in moderate doses, causes a very marked effect on the vision, as a result of which objects appear to be first violet in color and later yellow. This effect is known as xanthopsia. Disturbances of the senses of smell and taste may also occur. The urine contains a transformation product of santonin, santogenin (*Jaffe*), which in alkaline reaction colors the urine cherry-red. The dose of santonin ranges from 0.02 gm. up to the maximum dose of 0.1 gm. [*Forcheimer* states that he has seen death follow a dose of santonin in a child to whom it had been given on a suspicion of the presence of worms, although in reality this was not the case. He also states that 0.13 gm. has caused death in a child.—Tr.]

Thymol.—In the treatment of hook-worms, thymol is the drug *par excellence*. This occurs as large colorless crystals possessing an aromatic odor and pungent taste. [It is soluble in 1200 parts of water and in one part of alcohol, and fairly soluble in fats and oils and in alkaline solutions. Extensive experience in the treatment of this disease has shown thymol to be, when properly administered, a very certain means of causing the expulsion of these parasites, and that its use is unattended with danger if it be administered with the observance of certain simple and necessary precautions.

The dose should not exceed 4.0 gm., best administered in capsules containing about 0.5–0.7 gm. in finely divided form and triturated with milk-sugar. These should be taken on an empty stomach, and followed in from one to two hours by a promptly acting cathartic, preferably magnesium or sodium sulphate. For twelve hours before its administration and following its administration until the bowels have moved thoroughly, no fatty or oily food, or alcohol, should be taken. *Stiles* states that he has known of fatal results due to the administration of castor oil as a purgative following the thymol.—Tr.] One death, following the administration of 6 gm. to an anæmic individual, warns against its indiscriminate or careless use. [As a rule, only comparatively slight systemic symptoms should occur, and in fact with precautions even these occur but seldom. Its toxic action closely resembles that of carbolic acid.—Tr.]

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SPECIFIC DISINFECTANTS

The general antiseptics kill the protoplasm of all microbes as also that of the tissue cells. However, there are very distinct differences in the susceptibility of the different pathogenic and non-pathogenic varieties to the different antiseptics. This higher susceptibility of certain types forms, as it were, a bridge to the outspoken specific relationship between certain pathogenic organisms and certain cell poisons, on which depends the possibility of killing such parasites, even in the tissues of the host, without harming him.

Where such specific relationships do not exist, an internal disinfection is from its very nature impossible. Even in mucous membranes and wounds, general cell poisons cannot produce disinfection without severely damaging the tissue cells, and consequently it is absolutely impossible to utilize such general cell poisons as means of attacking the micro-organisms in the blood and in the interior of the tissues, because, on the one hand, the greater susceptibility of the central nervous system from the start prevents the use of higher concentrations, while, on the other, even those concentrations which are effective on the surface of wounds are not effective in the blood and in the tissues, for the disinfectant is diverted from the pathogenic organisms by the constituents of the body to a much greater extent when it is present in the general circulation than is the case in the secretions of wounds.

A striking example of the disproportion between disinfectant power in the reagent glass and in the organism has been furnished by the observations of *Bechhold* and *Ehrlich*, who discovered in tetrabrom-o-kresol and in hexabrom-dioxy-diphenylcarbinol two substances possessing extraordinary disinfecting power outside of the body and relatively slight toxicity. It was consequently possible to introduce these antiseptics into the bodies of animals in doses less than one-one-hundredth part of which would have been sufficient to prevent the further development of pathogenic bacteria (diphtheria) if they had been as effective in corpore as in vitro. However, these drugs failed entirely to cause an internal disinfection. This is explained by the fact that even blood-serum markedly lessened their disinfectant power, and in the body it is evident that the conditions were still more unfavorable for the absorption of the disinfectants by the bacteria.

This explains why, except in the case of specific drugs, internal disinfection fails, as does, for example, intravenous injection of corrosive sublimate which has been tried in various diseases of the lower animals. On the other hand, it is easy to understand why the attempts to obtain an internal disinfection have never been abandoned, for the effects of quinine in malaria and of mercury in syphilis certainly prove that such specific therapy is a possibility. Particularly against tuberculosis, specifics are constantly being recommended, but, unfortunately, only after insufficient investigation.

THE CREOSOTE TREATMENT OF TUBERCULOSIS has become of practical importance. The tar obtained from beech wood is one of the antiseptics longest known. From it is obtained, by distillation, a

dark yellow fluid with a smoky odor and burning taste—creosote. This is composed chiefly of guaiacol, the methyl ether of brenzcatechin, which, in pure form, occurs as colorless crystals, but which, as obtained in commerce, is usually a fluid differing from creosote chiefly in its less disagreeable odor. Guaiacol itself is a powerful antiseptic, but whether after absorption it can exert this action or whether it circulates in the blood in active combinations has not been definitely determined. It is excreted in the urine as an ethereal sulphuric acid.

In the mouth creosote and guaiacol cause burning and, when taken in concentrated solution, violent irritation of the mucous membranes, with vomiting and purging. Although guaiacol resembles the related phenol in these local actions, after absorption it is less toxic. When rapidly absorbed, as after subcutaneous administration, it, like other aromatic compounds, lowers the temperature [and acts as an analgesic.—Tr.]

After having been used to a large extent in France, creosote was introduced into Germany especially by *Sommerbrodt* in 1887, but was soon replaced by the purer and less irritant guaiacol. Numerous clinical observers testify to the fact that, when administered for a considerable period in increasing doses, up to one gramme per diem, it causes improvement of the appetite and nutrition, with gain in weight, and also exerts a favorable influence on the cough and expectoration. Perhaps a slight—quantitatively hardly measurable —amount is excreted through the lungs.

It appears to be impossible that without causing systemic poisoning one can attain a concentration of guaiacol on the blood and tissues which will suffice to kill the tubercle bacilli (*Guttmann, Cornet*) and even an inhibition of their growth by such means appears improbable, for, like other phenols, guaiacol is rapidly transformed in the body into antiseptically inactive conjugated sulphates. In case creosote and guaiacol actually do exert favorable actions in tuberculosis, these must be attributed to their indirect actions, perhaps because, like bitters, these drugs favorably affect the digestion and possibly also act as intestinal antiseptics. From this point of view it appears rational to attempt only a mild treatment with these drugs, and not the so-called intensive treatment, in which, by combining with their internal administration their administration through the skin and as inhalations, the endeavor is made to attain the highest possible saturation of the organism with guaiacol. Moreover, it should be remembered that the oral administration of large doses quite often causes disturbances of the digestion.

It is for this reason that at present the preference is given to the carbonates of creosote and guaiacol (creosotal and duotal), which are insoluble and consequently non-irritant in the stomach, but which are decomposed gradually in the intestine. Of similar preparations mention may be made of the valerianate of creosote (Eosot) and of

guaiacol (Geosot), potassium guaiacol sulphanate (Thiokol), a powder, of which the dose is from 2 to 5 gm. daily, and its solution, Sirolin.

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In various protozoal diseases it has been definitely shown that drugs may produce specific etiotropic actions, for quinine kills malarial parasites and certain arsenical compounds can kill trypanosomes and the Spirochæta pallida. The action of mercury in syphilis is another example of such specificity, and it is in the highest degree probable that salicylic acid also is an etiotropic curative agent, acting on the still unknown cause of articular rheumatism.

QUININE IN MALARIA

Through its action on heat regulation and metabolism, quinine is an antipyretic, which more or less efficiently controls pyrexia in various infectious diseases. Its almost universally curative effect in malaria is, however, due to altogether different causes, for here all the symptoms of the disease and not the fever alone are controlled by it. Here we are dealing with a typical example of specific etiotrophic therapy, for in doses which are harmless to man quinine damages and destroys most of the forms of the malarial parasites in the blood.

Up to the eighth decade of the last century it was generally assumed that in malaria quinine produced its effects through its action on the nervous system, but in 1867 *Binz* demonstrated the great susceptibility to this drug exhibited by certain simple protoplasmic organisms, and based on this the hypothesis that quinine cured malaria by acting directly on its cause, which probably would be found to be one of the lowest forms of living organisms. He further stated that quinine was much less toxic to the healthy cells of man than to this hypothetical cause of malaria.

The first objects used by *Binz* in these investigations were parameciæ, which were immediately killed by a one to four hundred solution, and whose movements were lessened by solutions of one to twenty thousand and entirely stopped after two hours, although these same infusoria were much more resistant to other alkaloids, such as morphine, strychnine, santonin, etc. *Binz* was able to demonstrate the same striking susceptibility to quinine in fresh-water amœbia, and also in the leucocytes of the blood, which in dilutions of one to fifty thousand cease their amœboid movements and undergo gross granular degeneration. On the other hand, other amœbia—for example, salt-water euglena—are much more resistant. Quinine is also a very powerful poison for various bacteria. From these various facts, *Binz* was justified in concluding that this drug acted as a specific.

The proof of the correctness of this theory of the manner in which quinine acted could be obtained only after *Laveran*, in 1880, discovered and recognized the Plasmodium malariæ as the cause of this

disease, and after this discovery had been confirmed by numerous investigators, when it was found that, even outside the body, the addition of quinine solutions to the blood rapidly kills the malarial organisms. All the investigations of the blood in malaria have shown that during the administration of quinine the parasites disappear from the blood, and that they may be recognized as persisting there only in those pernicious cases which are not cured by quinine.

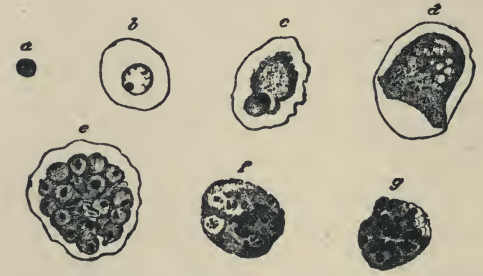

FIG. 61.—Tertian malarial parasites: *a–e*, normal; *f*, as affected by quinine; *g*, sporulation under influence of quinine.

In malaria the paroxysms of fever are due to the fact that the youngest forms of the sporozoa, the so-called sporozoits, which have penetrated into the red blood-cells and developed within them, after a time sporulate and leave the old corpuscles and penetrate into new ones. As it is in this phase of their life history that quinine is most toxic to these parasites, when given some hours before the expected paroxysm, it destroys them in large numbers and prevents the next paroxysm or moderates its severity in many instances, or at least prevents its recurrence. Tertian parasites are most susceptible to the toxic action of quinine, the quartan ones somewhat less so, and least of all those of the pernicious æstivo-autumnal fever, which sporulate almost entirely in the internal organs. It is stated that quinine is without effect on the gametes of the severer forms of malaria whose sexual cycle occurs only in anopheline mosquitoes. [This, however, is not true, for, although very resistant to quinine, the persistent administration of large doses of quinine causes the disappearance of these parasites from the blood, at any rate for a time, or at the least causes a marked diminution in their number (see *van Bezdorf*).—TR.]

Quinine muriate is usually administered in tertian and quartan malaria, three to five hours before the expected paroxysm, in doses of 0.3 to 0.7 gm., repeated two to three times at hourly intervals, and its daily administration in somewhat smaller doses should be continued for a considerable period after the disappearance of active malarial manifestations. In severe cases it is administered several times daily in doses of 0.6–1.0 gm. [In refractory or pernicious cases it should be injected intramuscularly, for which purpose the very solu-

ble bimuriate or the muriate of quinine and urea are the most suitable preparations.—Tr.] It has also been recommended that quinine should be given in broken doses, 0.2 gm. repeated five times daily, with the idea that in this fashion a regular and continuous absorption will occur and that a persisting action in the blood will result.

Quinine is slowly absorbed and at least in part remains in the blood in an unaltered form, for one-fourth to one-third of the amount administered in 24 hours is excreted unchanged in the urine (*Giemsa u. Schaumann, Nishi*). The remainder is destroyed in the organism. Its relatively slow excretion renders it possible to attain with permissible doses a constant concentration of quinine in the blood, which endows the taker with a certain amount of prophylactic protection against the sporozoits which may be introduced by mosquitoes. In addition to the symptoms of cinchonism already mentioned (p. 477), large doses at times cause hæmaturia or hæmoglobinuria, and it is probable that, particularly in patients severely ill with malaria, quinine causes the so-called black-water fever. [The evidence for and against quinine as a frequent cause of hæmoglobinuria is very conflicting, but it is reasonably certain that, while quinine is not responsible for all black-water fever occurring in malarial patients, it is often the final decisive factor in its production. This, however, does not constitute a contraindication for its administration in any cases of malaria, not even in cases with black-water fever, so long as the parasites may be found in the blood.—Tr.]

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SALICYLIC ACID IN ACUTE ARTICULAR RHEUMATISM

In all probability the action of salicylic acid in this disease is of an etiotropic nature, although this cannot be certainly maintained inasmuch as the pathogenic organism is not known. Probably the causative agent closely resembles streptococci and staphylococci, and, therefore, it probably is not of protozoal nature. Consequently, this drug may be looked upon as one of the group of general bacterial poisons which possesses specific curative properties. As these bacterial poisons are at the same time general cell poisons, and as salicylic acid is by no means very much more toxic to bacteria in general than it is to the susceptible tissues of the host, its utility as an internal disinfectant must depend on certain special conditions, as a result of which its toxic action on the central nervous system may be avoided while it may still be directed against the causative agent of rheumatism.

Free salcylic acid is scarcely less toxic to bacteria than is phenol, while it is at the same time strongly toxic to the tissues. On the other

hand, the salicylate of soda is a very feeble antiseptic and at the same time very slightly toxic to the tissues. As salicylic acid circulates in the blood chiefly or entirely in the form of its sodium salt, it is evident that after absorption it circulates about in a form which is but slightly toxic for the patient's tissues but at the same time also but slightly toxic for the bacteria. However, as shown by *Binz*, a rather high carbon dioxide tension sets free the active acid from the salicylates. While the CO_2 tension of normal tissues (about 6 per cent.) is not sufficient to do this, that of inflamed tissues, which may rise to 17.5 per cent. (*Ewald*), is amply sufficient. Even in the blood of asphyxia, containing about 12 per cent. CO_2, appreciable amounts of salicylic acid can be set free from its salts, and consequently it is possible that in inflamed joints a local antiseptic action may be exerted although the salicylate never reaches a harmful concentration in the other tissues, especially the nervous system.

After absorption salicylic acid is retained in the blood in strikingly large amounts and for a long time (*Jacoby u. Bondi*), and, while the bones contain very little, the muscles and particularly the joints contain much more. These findings also help to explain the fact that the action of this drug is to a considerable extent limited to the joints. These authors also found that in the joints of rabbits infected with staphylococcus aureus much larger amounts of salicylic acid were present than in those of the controls. These results indicate that this drug is especially attracted to and retained by the bacteria localized in the joints or by the substances produced by them in the inflamed tissue. Perhaps under these conditions the higher CO_2 tension plays a rôle in liberating salicylic acid, which on account of its solubility in lipoids penetrates into the cells and remains in them.

Therapeutic Employment.—In acute articular rheumatism sodium salicylate is administered in doses of 3.0–5.0 gr. per diem and in severe cases at the start in doses of 6.0–10.0 gr., which are reduced later. While as a result of its administration not only the fever but also the pain and swelling of the joints disappear, all too frequently such doses cause disagreeable side actions, resulting in the development of salicylism. On account of its irritating properties, free salicylic acid is no longer used internally. Inasmuch as the free acid is liberated from the salicylates by the gastric HCl, their administration may also cause symptoms of gastric irritation, which are only slightly lessened [? Tr.] by administering sodium bicarbonate with them. The neutral esters of salicylic acid which are decomposed only when acted upon by the intestinal ferments, however, do not irritate the gastric mucosa. This is the reason for one important superiority of phenyl salicylate, or salol, and of acetyl salicylate, or aspirin, and of other similar salicylic acid compounds.

Undesirable Effects.—In addition to gastric disturbances, buzzing in the ears is the most common undesirable effect of the salicylates.

Albuminuria and cylindruria are also caused, even by therapeutic doses of the salicylate of soda, but the evidences of renal irritation disappear after discontinuance of its administration (*Lüthje*). In pronounced salicylism, vomiting, excitement, vertigo, disturbances of vision, delirium, and even dyspnœa (*Quincke*) may occur, and very large doses may cause alarming slowing of the pulse and respiration with collapse and cardiac failure.

In mild poisoning it is sufficient to discontinue the drug, while in pronounced poisoning *Ehrmann* states that the administration of large doses of sodium bicarbonate may aid in causing the more rapid elimination of the salicylates.

These disagreeable systemic actions of the salicylates are due to too large amounts being absorbed at one time. After the administration of the rather insoluble esters, such as salol, the absorption occurs very gradually, for these preparations may reach even the lower portions of the intestines unaltered,—after very large doses salol appears in the fæces,—salicylic acid being liberated from them only gradually. As a consequence, after their administration salicylic acid is distributed throughout the body in a constant but low concentration. For this reason the curative effect of their administration is less striking and is produced more slowly.

Solol is usually administered in doses of 1.0 gm. five to six times a day. In the same fashion, when *acetyl-salicylic acid* (aspirin), acetyl paramidophenol (*salophen*), or salicylic acid, salicylic ether, (*diplosal*) is administered, it is easier to avoid the buzzing in the ears and the other undesirable side actions. *Methyl salicylates* and other fluid salicylic esters are applied locally to the skin, through which their absorption readily takes place.

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ACTION OF THE ARSENICAL COMPOUNDS ON PROTOZOA

The etiotropic action of quinine in malaria has shown that, in those pathogenic organisms which belong to the class of protozoa, the susceptibility toward specific poisons can be greater than that of the cells of the higher organisms, and that consequently such specific antiseptics may produce an internal disinfection without working injury to the host.

ARSENIC IN TRYPANOSOME DISEASES

Particularly useful in enlarging our knowledge of the specific etiotropic relations of this class of pathogenic organisms has been the

study of the experimental chemotherapy of the various trypanosome diseases. The causative agents of these diseases, to which the African sleeping sickness and numerous animal and human diseases of the tropics belong, may be readily and successfully inoculated into laboratory animals such as mice, so that trypanosomes in large numbers appear in their blood. In 1902 *Laveran* and *Mesnil* found that these organisms disappeared from the blood after the subcutaneous injection of .01 mg. of arsenic trioxide, and that mice, which otherwise would have succumbed to the infection inside of three or four days, continued to live for some time longer. Although after a time the parasites reappear in the blood, they may again be caused to disappear by repeating the administration of arsenic, but, unfortunately, the mice finally succumb to the repeated administration of this drug, the curative agent being, in comparison with its efficiency against the pathogenic organisms, too toxic for the host.

Organic Arsenic Compounds.—The further development of etiotropic arsenic therapy, which has, as its last achievement, led to *Ehrlich's* discovery of a new cure for syphilis, is built up upon the study of the manner in which complex metallic compounds act in the body. As has been previously explained, organic * metallic compounds, including those of arsenic, which do not contain the toxic element in an ionizable form, do not exert the direct toxic actions of their metallic constituents. For example, potassium ferrocyanide, whose solutions contain potassium ions and FeCy ions but not Fe and Cy ions, does not exert the direct toxic actions either of iron or of the cyanides, for in this complex compound they are not able to act as such, as they are present in it only in a masked form. So long as such complex compounds are not broken up in the body, they produce only their own peculiar pharmacological effects, but, when they are broken up so that the metallic ions are liberated, the effects of these latter are produced.

The ferrocyanide of potash is consequently very slightly toxic and, as it passes through the body unchanged, after its administration no secondary effects from its decomposition products may be observed. If, on the other hand, such complex compounds are decomposed in the body, the toxic action of metallic ions is sooner or later exerted, but, as a rule, they are exerted in different locations and with different intensity than when the simple ionizable compounds are administered. It is just this peculiar property of the complex organic metallic compounds which is decisive for their pharmacological value.

The points at which the organic compounds act and, at the same time, the nature of their effects and the order in which they appear depend on the physicochemical properties of the substances in ques-

* In this section, by organic compounds are meant such compounds as contain the metal firmly attached to carbon and consequently in non-ionizable form.

tion, these determining whether the complex compounds can penetrate into various organs and cells of the body, to which the simple ionizable metallic compounds penetrate either not at all or only in the course of very chronic poisoning, in which latter case they probably must first be changed within the body into very complex compounds. Not only the quantitative but also the qualitative differences observed between acute and chronic metallic poisoning are based on such considerations.

For example, in acute lead poisoning in man the symptoms consist essentially of those of gastro-enteritis and somewhat later of colic, while only after poisoning lasting weeks and months do the well-known lesions of the nervous and muscular systems develop. The same is true of experimental poisoning with simple lead salts. If, however, as in *Harnack's* experiments, an organic complex lead compound, like the triethylate of lead, be used to poison the animals, the result is very different, for, on account of its physicochemical properties, this substance very quickly penetrates into nerve and muscle cells and, after a rapidly passing peculiar molecular action, soon produces the same nervous and muscular lesions as are seen in chronic lead poisoning. It is thus evident that this complex compound has made it possible for the lead ions, which are contained in it and which later are liberated from it, to be distributed about in the body very differently from those ions which are contained in the simple inorganic lead salts.

In a similar fashion the diethylate of mercury, $Hg(C_2H_5)_2$, being a very stable compound, causes at first only very marked and characteristic toxic actions on the central nervous system, while the usual effects of mercury appear only very much later (*Hepp*).

The same holds good for the organic arsenic compounds, which, in accordance with their particular distribution in the organism, act on the tissues in situations which the ordinary arsenic compounds do not reach at all. It is this which is decisive for their value as drugs which will exert more or less elective toxic actions on pathogenic organisms.

Of these organic arsenic compounds, cacodylic acid has been widely used for therapeutic purposes,—for example, in phthisis,—while, since its recommendation by *Gautier* in 1896, it, as well as other organic arsenic compounds, has been used in the treatment of syphilis. Cacodylic acid, however, is broken up with too great difficulty, and consequently is not well adapted for the production of the etiotropic actions of arsenic.

Consequently, the stimulus was given for a search for organic arsenical compounds, which were sufficiently non-toxic and which could be absorbed and carried about in the organism in unaltered form, so that they might penetrate into the parasites, in which they might in some manner or other, probably in the parasites themselves, be transformed into products toxic for these parasites. The greatest value as etiotropic agents must be possessed by such organic compounds as are

but slightly absorbed or transformed by the cells of the host, but which either penetrate more readily into the pathogenic parasites or are more readily transformed by them into toxic substances.

Atoxyl.—Numerous experiments with etiotropic arsenic therapy were first conducted with arsenilic acid, or atoxyl, which was introduced into therapeutics by *Blumenthal* in 1902. First used in trypanosome diseases by *Thomas* in 1905, the value of this drug was proven by *Robert Koch* in his extensive experiments in treating the sleeping sickness. While atoxyl is in large part unaltered in the body and circulates about in the blood for a long time, enough of it is absorbed and transformed by the cells (*Igersheimer u. Rothmann*) to produce distinct effects. A certain proportion, varying with the species of animal used, is excreted unchanged in the urine (*Muto*), while the remainder is transformed in the body into powerfully toxic substances.

With the fixing of atoxyl or of its transformation products in the organs is combined the development of specific pharmacological actions, which are not produced by the inorganic arsenic compounds. Thus, in cats it causes disturbances of the central nervous system resulting in ataxia, spasms, and paresis, and, in dogs, renal hemorrhages and lesions in other internal organs (*Igersheimer*). In accordance with these actions, after administration of atoxyl, arsenic is found in the cat chiefly in the central nervous system, but in the dog chiefly in the internal organs (*Igersheimer u. Rothmann*).

In agreement with these experimental results, in man atoxyl all too frequently causes severe toxic effects, consisting in disturbances of the digestive system and nephritis, and in particular in toxic effects on the nervous system and on the eyes, as a result of which unpreventable progressive impairment of vision and permanent blindness due to optic atrophy may result from the use of atoxyl. For this reason it is of interest that arsenic may be found in the eyes of animals poisoned by atoxyl, but not in those of animals which have been poisoned by inorganic arsenic compounds and in which optic atrophy has not yet been observed (*Igersheimer u. Rothmann*).* These actions of atoxyl are probably to be attributed to its transformation products. Similar effects result from the administration of other substances closely related to it, such, for example, as acetyl-arsenilic acid. The maximum dose of atoxyl per dose and per diem is .02 gm.

Atoxyl when continuously administered must also in part be transformed into some inorganic arsenic compound or compounds, as, following its administration, symptoms of conjunctivitis, rhinitis, trophic disturbances of the skin, etc., occur, all symptoms which are characteristic of arsenic poisoning.

Atoxyl Derivatives.—Atoxyl has been shown by *Ehrlich* and *Bertheim* to be sodium paraminophenyl arsonate or arsanilate. This

*See page 537.

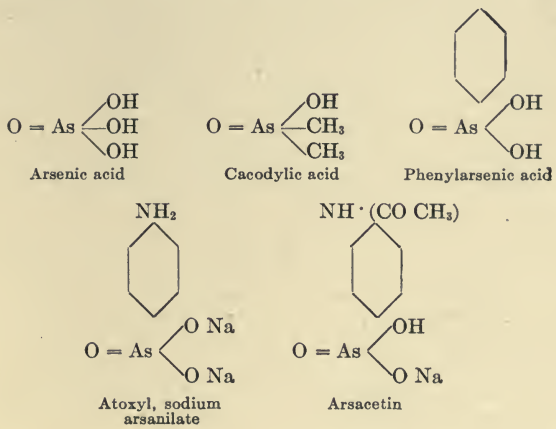
has served *Ehrlich* as a starting-point for extensive experimentation with a very large number of related compounds, which he obtained from atoxyl by changing its molecule—by reduction to compounds of trivalent arsenic and by the introduction of different side chains. As a test object for the curative value of these compounds in protozoal infections, animals infected with trypanosomes have been used.

The comparison of the efficiency of such substances has disclosed certain relationships between their constitution and the degree of their etiotropic actions (*Ehrlich*). Thus, **arsacetin**, obtained by the introdution of an acetyl radical into the amido group of atoxyl, was found by him to be more efficient than atoxyl. The maximal dose of this drug is the same as that of atoxyl (0.2 gm. per dose and per diem).

Neither arsenilic acid nor arsacetin kills trypanosomes in vitro, although arsenious acid and such organic arsenic compounds as contain trivalent arsenic do so, and it has been established that compounds containing pentavalent arsenic do not produce a direct effect on trypanosomes.

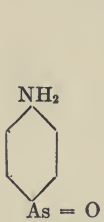
This is in agreement with earlier experience with arsenic compounds, for arsenic pentoxide is far less toxic to animal and vegetable organisms than arsenic trioxide, so that it has been assumed that the pentoxide as such is non-toxic and becomes toxic only after it is transformed into the trivalent ion (*Husemann, Loew*). The behavior of the trioxide and pentoxide of antimony is quite analogous.

Atoxyl and arsacetin are both compounds containing pentavalent arsenic, and it is probable that the curative action of atoxyl and of

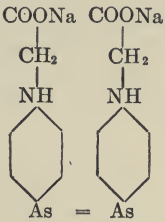


other organic pentavalent arsenic compounds depends on their transformation into compounds in which the arsenic is trivalent and which are directly toxic to protozoa (*Röhl, Friedberger*), just as arsenic pentoxide, according to *Binz* and *Schultze*, is in part reduced in the organism to arsenous acid. In para-aminophenylarsenous oxide, *Ehr-*

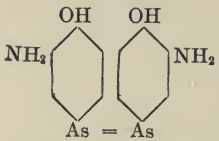
lich has prepared from atoxyl a reduction product which is directly toxic to trypanosoms and immediately toxic in the same manner as arsenous acid, while even large amounts of atoxyl when injected intravenously never produce toxic effects immediately but only after a rather long period of latency.



p-Aminophenyl-arsenoxyd



Arsenophenylglycin



Dioxydiamidoarsenobenzol

Although from the above facts it appears that all compounds of trivalent arsenic are much more toxic for the higher organisms than are those of pentavalent arsenic, it is possible, by introducing side chains into organic compounds of trivalent arsenic, to diminish their toxicity to such a degree that they are better borne by the experimental animals and still remain directly toxic to the protozoa. Thus *Ehrlich* and *Röhl* were able to cure even severe experimental trypanosomiasis by a single injection of **arsenophenylglycin** in dosage which was not dangerous for the host.

Other Specific Trypanosome Poisons.—Antimonial compounds, like those of arsenic, have also proven to be specific etiotropic remedies in trypanosomiasis. Moreover, at a period antedating the discovery of the arsenic therapy of these conditions, *Ehrlich* and *Shiga* discovered in **trypan red**, a dye of the benzopurpurine series, a drug which is very efficient against protozoa, and since then it has been found that **parafuchsin** and **tryparosan**, derivatives of rosaniline, even when introduced into the stomach, can cure experimental trypanosomiasis (*Röhl, Marks*).

If the trypanosomes reappear in the blood of the experimental animals after the curative effect of the organic arsenic preparations has passed off, by repetition of the injection they may be caused to disappear again, but only to return once more. Such parasites, from animals which have been repeatedly injected, when reinoculated into other mice, show themselves resistant to this remedy when it is administered to these new hosts.* Strains of parasites which have thus become resistant to arsenilic acid also show an increased resistance to other arsenic and antimony compounds, but not to the specifically toxic substances of the benzopurpurine and fuchsin series (*Ehrlich*).

ARSENIC IN SYPHILIS.

The Spirochæta pallida, the pathogenic organism of syphilis, discovered by *Schaudinn* and *Hoffmann*, is also a protozoal organism.

* Concerning similar augmentation of the resistance in infusoria see *Neuhaus*, Arch. intern. de Pharmacodynamie et de Therapie, 1910, vol. 20, p. 393.

The close biological relationship, which, according to *Schaudinn's* views, exists between trypanosomes and spirochætes, suggested the employment of organic arsenical compounds as etiotropic remedies in syphilis.* The first clinical curative results were obtained by the use of large doses of atoxyl (*Salmon,* 1907, *Lassar,* and others). *Uhlenhut* and his collaborators succeeded in experimentally demonstrating the efficiency of atoxyl in another spirochætal disease, the spirillosis of chickens, and soon after they were able to demonstrate the same for experimental syphilis. However, it appears that, in comparison with its toxicity for the patient, the specific etiotropic action of atoxyl on the Spirochæta pallida is too weak, for in human syphilis only large and dangerously toxic doses are effective.

Salvarsan.—*Ehrlich* attributes the much more powerful therapeutic action of salvarsan, dioxydiaminoarsenobenzol, to the radical containing the trivalent arsenic, the importance of which was rendered apparent in experiments with trypanosomes, and also to the introduction of hydroxyl radicals in the para position in the molecules, in which the amido radicals are in the ortho position relatively to the hydroxyl radicals (see formula, p. 536).

Hata was able to produce pronounced protective and curative results in numerous spirilloses with this preparation, as also with other arsenophenol compounds containing hydroxyl groups in the para position. Salvarsan rapidly caused the spirillæ of relapsing fever to disappear from the blood, and has shown itself a very powerful etiotropic agent in the spirillosis of chickens, in which disease the efficient curative dose was only 1/58 part of the largest non-lethal dose, while with atoxyl the curative dose was ½ of the lethal dose. In rabbits it was possible, by the subcutaneous injection of 1/7 to 1/10 of the largest non-lethal dose, to cause the spirillæ to disappear from the primary lesion in the scrotum as early as on the following day (*Hata, Tomasczewski*).

With salvarsan the ratio between the etiotropic efficiency and the toxicity is far more favorable than in all the other organic arsenic compounds thus far tested, and is particularly far more favorable than with atoxyl. This has thus far been confirmed by clinical experience in man, and in particular salvarsan does not produce the same toxic effects in the eye as does atoxyl (*Igersheimer*).† In animal experiments also it does not produce the symptoms characteristic of atoxyl and related compounds (*Igersheimer*).

This author was able, after salvarsan had been injected, to recognize the presence of arsenic in the syphilitically infected cornea of rabbits, but not in other portions of the eye or in normal eyes, a finding which indicates that the efficient arsenical compounds combine with the syphilitic tissues or with the spirochætes or their reaction products which may be present in such tissues.

In man the hydrochloride of dioxydiaminoarsenobenzol, or salvarsan, is injected subcutaneously and intramuscularly either in alkaline solutions or in neutral suspensions, and intravenously in alkaline

* For history of the development of this idea, see *Ehrlich,* Ztschr. f. Immunitätsforsch., etc., 1911, vol. 3, p. 1123.

† [In London, at the International Congress, *Igersheimer* reiterated this claim, and a careful search of the available ophthalmological literature has failed to show any case of such toxic action of salvarsan on the eye.—Tr.]

solutions. The intravenous injection acts most quickly and intensely on the symptoms of the early stages, but when injected subcutaneously it remains for a very long time at the place of injection, and when injected intramuscularly is somewhat more rapidly absorbed. In both of these latter cases it appears to form a deposit from which it is more or less regularly and gradually absorbed into the body, but, owing to the extreme irritation caused by its long-continued contact with the tissues, such injections cause severe and persistent pain, with lasting infiltration and often extensive necrosis. Consequently, *Ehrlich* more recently recommends that it be administered in alkaline solution exclusively by the intravenous route in doses ranging up to 0.6–0.8 gm.

It would appear that a general internal disinfection may be more certainly obtained by a single or several times repeated injection of salvarsan than is attained when it is injected subcutaneously or intramuscularly, in which case it forms a deposit from which it is very gradually absorbed. This is in accord with the experience obtained in animals, that the parasites which have withstood the first attack of the remedy acquire a relative immunity to it.

After intravenous injection salvarsan is eliminated rather rapidly, but when injected subcutaneously, while the elimination starts very soon, it continues for about fourteen days, and after intramuscular injection somewhat longer (*Greven*). After intramuscular injection chickens remain immune to infection with spirillosis for 30–40 days, but after intravenous injection the protective effect disappears in 3–4 days (*Hata*).

That salvarsan exerts an etiotropic action on human syphilis is indicated in the first place by the rapid disappearance of the spirochætes following its injection. In addition, this is indicated by the fact that the blood-serum of patients treated with salvarsan appears to contain specific antibodies which exert a curative effect in children with hereditary syphilis (*Scholtz* and others). According to *Ehrlich,* the formation of these antibodies is due to the destruction of the parasites by this remedy, their decomposition products stimulating the organism to form antibodies; but, according to *Friedberger,* salvarsan itself directly and markedly stimulates the formation of antibodies.

Salvarsan has also proven itself an efficient etiotropic remedy in other spirochætal diseases, particularly in relapsing fever (*Iversen*).

This is not the place to enter into a discussion of the respective fields and limitations of salvarsan and mercury in the treatment of syphilis. A combined alternating treatment with these two remedies * would appear to be theoretically indicated by the experiences obtained by "combination therapy" in experimental trypanosomiasis and spirochætal infections (*Tsuzuki*). These have shown that the combination of several etiotropic substances produces a more energetic

* [Practical experience has proven the correctness of this theory.—Tr.]

effect and a more certain cure than would be expected from the arithmetical sum of the effect of the different substances used. Such alternating treatment with arsenical and mercurial preparations would appear to be indicated by the fact that the resistance acquired by certain protozoa to one group of etiotropic remedies does not extend to remedies of a different nature, and consequently it is probable that those parasites which have become resistant to one remedy and which are responsible for recidivation may be destroyed by remedies of a different nature.

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MERCURY AS A SPECIFIC FOR SYPHILIS

Historical.—Mercury has long been considered a specific against the secondary symptoms of syphilis. After having been used even earlier in the Orient, mercurial preparations about the year 1500 became generally recognized as efficient in syphilis when administered internally. At this time mercury was pushed up to the appearance of severe toxic symptoms, such as salivation, diarrhœa, etc., so that the dangers which accompanied the treatment soon led to a reaction, as a

result of which physicians in the sixteenth century were divided into the two camps of mercurialists and anti-mercurialists. Gradually, however, this opposition, which persisted even into the nineteenth century, has disappeared as physicians have learned how to use the remedy rationally.

Its Etiotropic Action.—That mercury exerts an action on the causative agent of syphilis is rendered probable by the fact that the most varied symptoms of the infection are equally influenced by it and that healthy children may be born of syphilitic parents who have been treated with mercury, while, when the parents have not been treated by mercury, their children are congenitally syphilitic. Thus far it has not been definitely proven that this action on the Spirochæta pallida is etiotropic in the same strict sense as is the action of quinine on malarial plasmodia, for an indirect action on these parasites by stimulating of the formation of antibodies is conceivable. However, it is more probable that this drug acts directly on the pathogenic organisms, for, in general, cures result the more certainly, the more completely and persistently the body of the patient is kept saturated with mercury to the degree of tolerance. It is a recognition of this fact which has led to the general adoption of the chronic intermittent mercury treatment, in which the infected individuals are kept under the influence of mercury off and on for several years.

The excretion of mercury in the urine offers a means of estimating the amount of mercury circulating in the body and the duration of its action. While after absorption mercury circulates about in the body as a compound of mercury-albuminate and sodium chloride, and is chiefly excreted in the fæces and to only a small extent in the urine, still that portion of the mercury which is present in the general circulation, and which passes through the renal vessels, probably maintains a definite ratio to the amount excreted in the urine. The more rapidly the mercury appears in the urine after its administration in the given method the more rapidly and intensely are its effects produced, and the more rapidly its elimination by this channel diminishes the more rapidly does its action in the body pass off. Always, however, it continues to be excreted for months, and, under certain circumstances, after the urine has become free from mercury it may appear in it again, both of these facts proving that mercury is stored up in different organs, as a result of which poisoning must sooner or later result if the elimination fails to keep pace with the absorption.

The aim of every energetic antiluetic mercurial cure must be to maintain for a considerable time the mercury content of the organism at such a height that, while not causing toxic effects, it remains not too far below this toxic concentration. A regular elimination of mercury during the period of administration and a gradual sinking of the curve of elimination after its cessation may serve as signs that one is close to the attainment of such saturation. A temporary marked

increase in the amount eliminated, either directly after its administration or in the course of the cure, indicates a too rapid absorption, with its accompanying danger of poisoning.

The determination of the **curve of elimination** *is, consequently, of importance for the determination of the value of different methods of administering mercury (Bürgi).*

When **mercurial inunctions** are given (of mercurial ointment 33 per cent., daily 3.0–5.0 gm. for 30–40 days), mercury may be recognized in the urine from the first day on, its elimination increasing gradually up to a certain point and then remaining for weeks very nearly constant, and, after cessation of treatment, falling again very gradually. The absorption of mercury from the ointment is due in part to the gradual change of the metal, which has been pressed into the openings of the ducts of the glands of the skin, into mercuric salts of the fatty acids, or to its gradual change into these same salts by the oxygen of the air acting under the influence of the secretions of the skin. As this chemical transformation occurs very gradually, local irritation does not, as a rule, occur. The mercury is also to some extent absorbed through the lungs as a result of respiring such of it as is vaporized by the body heat.

By Inhalation.—When present on the surface of the skin, metallic mercury vaporizes in sufficient quantities to produce therapeutic effects solely as a result of its absorption through the lungs. On this fact is based the employment of mercurial amalgam, a gray powder composed of aluminum and magnesium amalgam, which is kept in contact with the skin in a small bag and thus provides a mild mercurial treatment. When thus used its elimination follows essentially the same course as in a mild inunction cure.

Oral Administration.—When mercury is to be administered by mouth, the mercurous compounds are usually employed, particularly calomel, HgCl (0.03–0.05 gm. ter in die, at times combined with opium), and the yellow iodide of mercury, which is used in the same dosage as calomel, and which is particularly often used in children, in a dosage for infants of 0.01 gm. per diem. Although in vitro the mercurous compounds are insoluble in water, in the body they are absorbed, but when they are administered internally the amount of mercury eliminated in the urine shows very marked variations from day to day, due apparently to the varying conditions affecting absorption from the intestine. The suddenly increased absorption which may occur when Hg is thus administered explains the greater danger of causing mercurialism when mercury is administered internally, and when it is thus administered stomatitis and diarrhœa are observed relatively often.

For **mercurial injections** soluble and insoluble preparations are used.

Of the **soluble** ones the bichloride is the one most used, in daily small doses of 0.01 gm. continued for 20–40 days. Its excretion in the urine starts at once, and if the injections are given each day the

amount eliminated rises gradually and regularly just as is the case in inunction cures, and when its administration is stopped the amounts eliminated gradually decrease, its elimination curve corresponding to that of a gradual saturation. Unfortunately, these injections in many cases cause pain and induration, even when by addition of sodium chloride the attempt is made to prevent the precipitation of mercury albuminate at the point of injection.

These local effects cannot be certainly avoided, even by the use of organic compounds of mercury with formamide, glycocoll, etc., which are soluble in alkaline media.

Finely divided **insoluble** mercurial preparations, such as calomel, thymol-acetate of mercury, salicylate of mercury, etc., are injected (suspended in liquid paraffin or olive oil) in amounts of 0.05 to 0.1 gm., at considerable intervals,—about every six to seven days,—with the idea of forming a deposit of mercury from which absorption will take place gradually. As a matter of fact, however, the elimination curve after injection of the widely used salicylate of mercury does not indicate a gradual regular saturation of the organism with mercury, but, on the contrary, the maximal elimination occurs on the day of injection and sinks immediately, rising with each new injection. This curve of elimination is in accordance with the clinical experience that, although these injections are very efficient, they are at times dangerous, for a serious poisoning may result from the unexpected sudden absorption of large amounts of mercury from the reactively inflamed tissues around the mercurial deposits.

After **intravenous injection** of the bichloride, the curve of elimination rises abruptly and falls again very quickly. When thus administered more than 50 per cent. is rapidly eliminated from the body, and for a time so much mercury is present in the circulation that the danger of causing toxic symptoms is necessarily great, not to speak of the danger of the formation of thrombi.

From the above it is apparent that inunction cures best meet the demand for a gradual and even mercurialization. [The translator is among those who are convinced that hypodermic injections of soluble mercurial preparations have been proven to be the most rapid and certain means of curing syphilis by mercury. The observations on the disappearance of the Wassermann under various methods of treatment, as well as the observations on its reappearance or failure to reappear, both appear to indicate that this conclusion, which has been based on clinical experience, is well founded.—Tr.] However, even when mercury is thus administered, it is not always possible to avoid the symptoms of poisoning. These start with a metallic taste in the mouth, stomatitis, and salivation (see p. 513). Albuminuria and nephritis * may also develop during mercurial cures, and in severe poisoning diarrhœa occurs. In fatal cases cardiac depression, sinking of the blood-pressure, and collapse may result.

* [Albuminuria and nephritis are not infrequently manifestations of syphilis, the occurrence of which during the mercurial cure is, the translator believes, quite as often, or more often, due to the disease than it is to the remedy.—Tr.]

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ANTITOXINS

Historical.—The experimental therapy of infectious diseases had its origin in the study of the problems of immunity.* In his studies of acquired immunity *Pasteur,* having observed that many infectious diseases attack the same individual but once and that in such cases a very light attack appears to give the same protection as a severe one, started a series of logically planned laboratory experiments in the hope of finding methods of treatment which, like light attacks of illness, would give the same immunity without injuring the animals experimented on. He strove to reach the same goal as had been attained empirically by *Jenner* when he utilized the chance observation that the harmless cowpox protected against the dangerous human smallpox.

In 1880 *Pasteur* succeeded in immunizing animals against the virulent pathological organisms of chicken-cholera, and soon afterwards of anthrax, by inoculating them with artificially attenuated bacteria. The discovery that the virulence of microbes may be increased or diminished by their passage through animals was of great importance in *Pasteur's* later success in discovering his method of inoculation against rabies. The Americans, *Salmon* and *Smith,* while investigating hog-cholera, 1885–86, were the first to learn that immunization could be produced by injecting not only attenuated bacteria, but also their soluble metabolic products, known to-day as toxins. Later on, immunization against the bacilli of tetanus and diphtheria was accomplished by *Roux* and by *Brieger* and *Kitasato,* who injected filtrates from bacterial cultures for this purpose. While in other cases it was not possible to produce immunity by use of the metabolic products of living bacteria, if the bacteria first be killed, it is possible to produce immunity by injecting the substance contained in the dead bodies, the endotoxins. This was first done by *Pfeiffer* using cholera vibriones.

Further progress in the study of the problems of immunity was rendered possible by the discovery that the inoculation of animals with gradually increasing amounts of bacterial substances produces an immunization not only against the living pathological organisms, but also against the injection of large quantities of the same extremely toxic substances with which they are inoculated. As a result of the recognition of this fact, it became possible to investigate these problems by quantitative methods.

* In this connection the authors will confine themselves to a discussion of those points bearing on immunization which are essential for the understanding of the now generally adopted method of treatment. More complete discussions may be found not only in various monographs and larger works, but in the following works: *Krehl u. Levy,* Kap. Infektion und Immunität in *Krehl's* Pathol. Physiologie, 5. Aufl., Leipzig, 1907; *M. Jakoby,* Immunität und Disposition, Wiesbaden, 1906; *Oppenheimer,* Toxine und Antitoxine, Jena, 1904; *Th. Müller,* Infektion und Immunität, Jena, 1904; *Dieudonné,* Immunität, Schutzimpfung und Serumtherapie, 6. Aufl., Leipzig., 1909.

Active and Passive Immunity.—Soon after *Pasteur, Chauveau,* in 1881, showed that it was possible to produce immunity by the injection of living pathogenic organisms of full virulence, for the natural protective powers of the organism are able to maintain the upper hand in the strife against bacteria, providing the number of these be small or if the conditions for their multiplication be unfavorable. If the organism overcomes the infection or the poisoning by toxins, it becomes immune as a result of the activity of its own protective mechanisms, which form antitoxin and other protective substances. This type of immunity, resulting from the activity of the organism itself, is known as active immunity, the specific immune bodies thus formed circulating about in the blood, as has been known ever since *Behring's* discovery of the antitoxins. Passive immunity, which results from the introduction into an animal of such already formed immune substances, is thus named because it is produced without any aid from the individuals rendered immune.

While in active immunity a certain period, usually from five to ten days (*v. Dungern*), must elapse before the development of immunity, passive immunity is conferred immediately by the administration of the protective serum. Active immunity persists for a very long time, as those reactions of the cells which result in the formation of the immune bodies persist for a long time and endow the organism with the power of making good the loss of its protective substances. Passive immunity, on the contrary, persists for a much shorter time, for the substances which have been derived from actively immunized individuals are foreign substances for the passively immunized organism, and are therefore eliminated or combusted and are not replaced by the organism.

In human medicine, except for vaccination against variola and more recently against typhoid, active immunization is employed only for the treatment of rabies.

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VACCINATION AGAINST RABIES

This disease, the pathogenic organism of which is not yet known, is remarkable for its long period of incubation; but *Pasteur* discovered that the period of incubation may be very strikingly shortened by injecting the virulent substances, obtained from the central nervous system of rabid animals, directly into the central nervous system instead of into other parts of the body. This shortening of the incubation depends, as we know to-day, on the fashion in which the toxic substances are distributed throughout the body, for these reach the point at which they act, the central nervous system, through the peripheral nerves, the disease developing only when the poisonous substances have reached these centres.

These findings of *Babes* and of *de Vestea* and *Zagari*, however, left it unsettled whether it was the pathogenic organisms themselves or the poisons produced by them which thus travelled along the nerves. Since, however, *Hans Meyer* and *Ransom* have shown that tetanus and diphtheria toxins are carried to the central nervous system by the nerves, it may be assumed that direct inoculation of the rabies virus into the central nervous system shortens the period of incubation, because in this case the poison itself does not have to pass along these paths. The more virulent the virus the more rapidly is the toxin manufactured, and consequently the shorter is the period of incubation, but even with the most virulent virus a certain length of time is needed for the journey to the central nervous system, varying with the length of the nerve path and amounting in the rabbit to 7–8 days and in the guinea-pig to 5–6 days.

By appropriate passage of the virus through a series of animals or by heating it in the absence of moisture for varying periods, *Pasteur* obtained viruses of varying virulence and incubation period, and, by inoculating animals first with the weak viruses, he was finally able to render them actively immune against the most virulent viruses. In animals thus actively immunized the blood contains protective substances, for when such serum is inoculated into other animals it protects them also (*Babes et Lepp*). Owing to the fact that the rabies organism is unknown,* it cannot to-day be stated whether these protective substances protect against the toxins produced by this organism or against the organism itself (*Marx*).

In any case the efficiency of the Pasteur prophylactic treatment of rabies is to-day established beyond question. As the treatment is necessarily always inaugurated only after infection has occurred, it is evident that the protective substances which are produced during immunization must reach the toxins manufactured at the point of infection before they are carried to and become combined with the nervous centres. When the treatment is instituted promptly this is possible, probably because the multiplication of the pathological organisms and the manufacture of the toxins at the infected point go on very slowly.

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TUBERCULIN

Tuberculin treatment is also based upon active immunization (*Sahli*). The various tuberculins are endotoxins which may be ex-

* [Recent investigations by *Moon*, *Noguchi*, *Poor* and *Steinhard* and *Williams* make it probable that this organism is no longer to be numbered among the unknown pathological agents. *Moon* and *Harris* both report curative effects from quinine in this disease.—Tr.]

tracted from the bodies of the bacteria only after their death. The various preparations used in practice either, like old tuberculin, contain those constituents of the dead bacteria which are soluble in glycerin and water, or, like new tuberculin, they consist of a suspension of very finely pulverized dead bacterial bodies. With new tuberculin *Koch* has been able to immunize animals against ordinarily lethal infection with tubercle bacilli.

When introduced into the body tuberculin causes both a systemic reaction and one localized in tubercular tissues. It is the different intensity of the reaction produced by tuberculin in normal and in tubercular animals and human beings which is responsible for the clinical significance of the various diagnostic tests (*Koch*). While tubercular tissues exhibit a similar hypersusceptibility to certain other substances, such as cantharidin and the albumoses, still there are quantitative differences which make it apparent that the reaction of tuberculin is a specific one (see p. 490). This specifically altered susceptibility is known as allergy, and in the case of tubercular tissues is attributed by *v. Pirquet* and *Schick* to the presence of a specific antibody for tuberculin (*Moro*). According to *Wolff-Eisner*, this antibody sets free from the tuberculin certain substances which produce an augmented endotoxin action.

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SERUM THERAPY

Serum therapy depends upon the fact that protective substances, which have been formed during active immunization in one animal, may be injected into a second one (a human being). Before discussing the principles of serum therapy and the limits of its efficiency, it will be necessary to describe our present conceptions of the nature of toxins and antitoxins and of their reciprocal relationships.

Toxins.—The conception of toxins arose when powerful toxic substances were found in the pathogenic micro-organisms and their toxicological significance was recognized. At the start there were found in the filtrates from bacterial cultures soluble poisons, which produced the same symptoms as the pathogenic organisms themselves (*Roux et Yersin, Brieger u. Fränkel*). Later substances with similar toxic properties were found in the bodies of the bacteria and also in certain poisons of animal origin and in certain vegetable seeds. These were at first thought to be true proteids, because they could be precipitated from their solutions along with the proteids also present therein. However, we actually know nothing of their true chemical nature, as

no one has thus far succeeded in preparing toxins in pure form and consequently our conception of the toxins is only a biological one.

These toxins are poisonous substances possessing the power of stimulating the organism to form specific antidotal poisons or antitoxins. We know of them that they diffuse with difficulty or not at all, and that consequently they are either themselves colloidal substances or, as a result of combination with proteid substances, have acquired colloidal properties. Most of them are very susceptible to heat and light and to exposure to air and are chemically very labile. It is very possible that they actually are proteids, for their most characteristic property, that of stimulating the organism to form specific substances which react with them, is also a property of non-toxic proteids in so far as these reach the blood without being denatured. Moreover, like the proteids, the toxins are acted on by enzymes or ferments, a fact which, taken with the slight absorption of some of them, explains their relative harmlessness when swallowed.

Toxins also show very close analogies with the ferments, of whose chemical nature we know quite as little. These, too, excite the production of specific antiferments in the organism, and are characterized, like the toxins, by the property of exerting their actions only on certain specifically susceptible substances. Like the ferments, the toxins also are perhaps protoplasmoid,—that is, they too may possess certain properties of living proteid.

From the above it may be seen that our knowledge of toxins is limited to a knowledge of their toxic actions and of their power of stimulating the body to form specific antitoxins. As already mentioned, poisons of this type are formed not only by bacteria, for certain poisons of animal origin behave in an entirely similar fashion,—for example, the venom of certain toads, spiders, snakes, scorpions, and bees, and many toxins derived from fishes. In addition, similar substances, known as phytotoxins, occur in plants,—for example, ricin in ricinus beans, crotin in croton seeds, and abrin in jequirity beans.

Antitoxins.—The antitoxins were discovered in 1890 by *Behring* and *Kitasato,* who showed that animals could be immunized by the injection of the blood-serum of other animals which had been actively immunized against tetanus and diphtheria. Soon after, in 1891, *Ehrlich* showed the same for ricin poisoning. As the serum of the actively immunized animal does not contain even traces of toxin which could produce active immunity in the second animal, it was evident that during active immunization a new substance must have been formed either out of the original toxin or from the body cells or from both together. This new substance acts specifically with the toxin which has been used to produce active immunization, and with no other.

Nothing is known of the chemical nature of these antitoxins, but it is practically certain that they are colloids of distinctly greater

molecular weight than the toxins, for they diffuse much more slowly than do these (*Arrhenius, Madsen*). Antitoxins, too, are chemically labile, although in general more stabile than the toxins, and many of them are not destroyed by heating up to 60° C., and even, depending upon the amount of salt present in their solutions, up to nearly 80° C. They are also more resistant than the toxins to the action of acids and alkalies, and are not so readily decomposed by exposure to light and air.

From the above it is clear that the antitoxins also can be characterized only biologically. They are reaction products of the organism which are produced under the influence of toxins, and which act specifically with and render harmless only the toxin which has stimulated their formation. We know nothing of their other actions in the body.

The Specificity of the Reaction between Toxins and Antitoxins.—In vitro the blood-serum of an animal immunized against diphtheria can render harmless only diphtheria toxin, but not tetanus or other toxins, and can protect other animals only against lethal doses of diphtheria toxin but not against those of other toxins. To explain this it might be assumed, with *Buchner*, that both antitoxins and toxins react with those body cells which are susceptible to the toxins, and that the antitoxins when injected previously to or simultaneously with the toxins are able to interfere with the action of the latter by a physiological antagonism. To-day, however, we know that *Ehrlich's* and *Behring's* view is the correct one, and that the antitoxin exerts no direct action on the body cells but reacts only with the toxin. In this reaction the toxin is not destroyed by the antitoxin, as was at first believed; but the reaction between the two substances consists rather in a reciprocal fixation or combination which takes place in accordance with fixed quantitative conditions, as has been shown by *Ehrlich* for ricin and diphtheria toxins and their antitoxins. This reaction needs a certain time for its completion and proceeds more rapidly at high temperatures than at low. Whether the combination between toxins and antitoxins is to be conceived of as analogous to the combination between weak bases and weak acids, or whether the toxin-antitoxin reaction is reversible only with difficulty or not at all, is still the subject of active discussion (see *Arrhenius*).

That the detoxication of toxins by antitoxins is actually due to the formation of a non-toxic compound is proven by the fact that in certain cases it is possible to separate the toxin and the antitoxin from the compound which has been formed. Thus, *Roux* and *Calmette* were able, by boiling a non-toxic mixture of snake venom and antitoxin, to render it poisonous again, for this antitoxin is readily destroyed by boiling while the venom supports high temperatures much better. Further, *Morgenroth* has recently succeeded in separating diphtheria toxin from its combination with the antitoxin by allowing acids to

act upon the compound. Finally, in certain cases either the free toxin or free antitoxin diffuses through certain membranes, although the mixture of the two is unable to do so (*Martin* and *Cherry*).

Formation of Antitoxins.—The manner in which antitoxins are produced is entirely unknown. Their specificity suggested that they were formed from the toxins (*Buchner*),—that is, that the organism had the power of changing the toxins into antitoxins, which could render harmless toxins subsequently administered. If this were so, however, one would expect that there would be some quantitative relationship between the amount of toxin administered and of the antibodies formed. *Knorr,* however, has shown that, after the injection of a certain amount of tetanus antitoxin, the body produced enough antitoxin to neutralize 100,000 times as much toxin as had been administered. Further, *Roux* and *Vaillard,* by repeatedly bleeding horses immunized against tetanus, have been able to remove from them amounts of blood equal to the total original blood content of the animals, without materially lessening the antitoxic power of the blood-serum. It is also known that other antibodies related to the antitoxins, such as the agglutinins present in the blood-serum of men who have recovered from typhoid, may be demonstrated in these individuals for months and years, although the fate of the already formed antibodies introduced from without shows that they are gradually destroyed or eliminated and disappear entirely. It is, therefore, clear that in actively immunized animals the antitoxins must continue to be manufactured for a very long time. Thus, the quantitative disproportion between the toxin administered and the antitoxin produced and the continuation of the formation of antitoxin without further administration of toxin both render it highly probable that the antitoxins are products of the metabolic activity of the cells.

Antitoxins are, therefore, to be looked upon as produced by specific but still completely unexplained active processes in the body cells, which are excited by the toxins. Once these reactions have been inaugurated, they may persist much longer than their inaugurating stimulus, and, as is the case with other effects of stimuli, there is not necessarily any fixed proportion between the amount of toxin administered and the products of the reaction thus excited.

Practically nothing is known as to the place where antitoxins are formed. The blood is looked upon simply as the place where they accumulate, but not as the place where they are formed. Of the various organs it has been possible only to show that the lymphoid tissues contain protective substances at the commencement of active immunization before these may be detected in the serum (*Pfeiffer u. Marx, Wassermann, Römer*).

Antigens and Antibodies.—The formation of antitoxin is only a special instance of a general reaction which follows the entrance into the blood of proteid substances which have not been denatured, for it is a general rule that, when such substances penetrate into the blood,

the organism forms reaction products which react specifically with them. Thus, after the parenteral introduction of heterologous proteids,—whether these, like the proteids of bacteria, are toxic, or whether, like heterologous serum, albumen, lacto-albumen, etc., they are relatively non-toxic,—precipitins appear in the blood-serum, which react specifically with the proteids in question and form insoluble products with them. When bacteria are injected, bacteriolysins are formed, and, when normal cells are injected, specific cytolysins or agglutinins. In these instances the reaction between the antibodies formed in the blood and the antigens—that is, the foreign substances which excited the reaction—are directly visible. The presence of other antibodies, as these specific reaction products are generally named,—for example, that of the antiferments,—may be recognized in the serum only by the fact that they inhibit the activity of the antigens,—*i.e.*, in the case of the ferments they inhibit their ferment action. In the same way the presence of antitoxins is recognizable only from the fact that the serum prevents the toxic action of the toxins.

EHRLICH'S SIDE-CHAIN THEORY

While we actually know nothing of the manner in which antibodies are produced, according to the views advanced by *Ehrlich* and now accepted by most investigators, the antibodies normally exist as "side-chains" in the cells which produce them. According to the hypothesis, certain atom groups of the protoplasm react with the antigen introduced, and these same atom groups under the influence of the reaction are manufactured anew in increased amounts and pass into the blood as soluble reaction products which act as antibodies. So long as these reacting protoplasmic groups remain combined with the cells, they attract the antigens to the cells,—*i.e.*, they attract the toxins to the point at which they exert their toxic action. When, however, they are present in the blood as antitoxins, by their affinity to the toxins they divert them from their point of reaction, the specifically susceptible elements in the cells.

Toxoids.—A matter of great importance in the further development of the theories of immunity was the behavior of certain substances which are readily formed from the toxins, and which, while relatively non-toxic, are still able to combine with antitoxin.

Ehrlich, during his investigations of diphtheria toxins, was the first to find such substances, named by him toxoids. This author found that there was a parallelism between the toxic action and the power of combination with antitoxin only in freshly prepared solutions of diphtheria toxins, and that, when the solutions were allowed to stand for a time, their toxicity decreased, but their power to neutralize antitoxin persisted, as did that of stimulating the formation of antitoxin. To explain these facts *Ehrlich* assumes two types of atom groups in the toxin molecule,—a combining or haptophoric group, by which the toxin is anchored to the cell protoplasm and by means of which it combines with antitoxin, and a toxophoric group, the loss of which robs the toxin molecule of its typical toxic actions. These toxophoric groups are lacking in the toxoids, which, however, through their haptophoric groups are still able to attach themselves to the

protoplasm of the cells, thus stimulating the production of antibodies, and to react with the antitoxin in the same way as the entire original toxic toxin molecule.

This parallelism, between the capacity of combining with antitoxin in vitro and that of exciting the formation of antitoxin, led *Ehrlich* to assume that the same atom groups are responsible for the combination of antigen with antitoxin and for its reaction with the cells of the organism, and, according to his theory, this stabile combination between toxin and cell protoplasm is the cause of the production of antibodies, while the typical toxic action of toxin has nothing to do with it. The fact that the production of antibodies may be excited by toxoids as well as by toxins is thus explained, as is also the fact that the toxins excite their production only in case the cells are not too severely damaged by their toxic action. In accordance with this assumption, those cells which have not been at all damaged by the specific toxic action of the toxin can also take part in the production of antitoxin, if the toxin simply combines with their protoplasm.

It is thus apparent that, according to *Ehrlich's* side-chain theory, the antibodies are those atom groups of the protoplasm which react in the cells with the antigens and are then formed in excessive amounts and cast off into the blood. This theory, however, does not tell us why the superfluous new formation and casting off of side chains occurs during the manufacture of antibodies. *Ehrlich* himself draws an analogy between the phenomena resulting from damage to the protoplasm by foreign substances and the morphological phenomena observed following trauma of the tissues, in which not only the cells which have perished are replaced but in which there always occurs a distinct over-production.

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ANTITOXIC SERA

Antitoxic sera are employed in the treatment of diphtheria, tetanus, dysentery, and snake bites. Practically the most important point in connection with their preparation is the securing of the highest possible percentage of antitoxin in the serum of the immunized animals. By quantitative experiments, *Ehrlich* has been able to show that the higher an animal is immunized the larger the amount

of antitoxin accumulated in its blood. After a latent stage of about 5 days the antitoxin content of the serum progressively increases until the maximum is reached, with diphtheria at the end of 10 days and with tetanus at the end of 17 days, after which the antitoxin content sinks, to rise again after some weeks and then to remain constant for a long time.

When the immune serum is injected subcutaneously into a second organism, the antitoxin is slowly absorbed and remains in the blood for a considerable period. Thus, *Knorr* found that tetanus antitoxin attained its highest concentration in the blood only at the end of 24–48 hours after the injection, and that the concentration then sank gradually so that it disappeared from the blood at the end of three weeks.

It is thus seen that, while passive immunity never lasts so long as active immunity, a single injection of diphtheria or tetanus serum still confers a protection lasting for several weeks. This relatively long stay of the antitoxins in the blood renders it probable either that they are chemically closely related to the normal blood proteids or that they circulate about in the blood in combination with proteids (*Römer*). *Ehrlich* has shown that milk contains antitoxin, and that consequently protective substances may be transferred from the nursing mother to the infant.

Limits of Their Curative Powers.—While the antitoxins are present in all the body tissues, although in slighter quantities than in the serum, they probably do not penetrate into the interior of the cells. This is the case, at least, with a number of the most thoroughly studied antitoxins,—for example, the tetanus antitoxin and probably also the diphtheria antitoxin. This inability of the toxins to follow the antitoxins into the cells determines the limit of the curative action of a serum when once the illness has developed. Probably the antitoxins are not able to exert any curative effects on damage which has already been suffered by the cells which are susceptible to the toxins, but are able only to prevent their further permeation with toxins and thus to prevent any further damage to the tissues. In the sections on the serum treatment of tetanus and diphtheria, the effects of the serum treatment of such conditions will be further discussed.

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TETANUS

In this disease the characteristic symptoms are not caused by a general invasion by the pathogenic agents, but result from the absorption and distribution of the soluble toxins which are formed at the site

of the infection. Consequently, in animal experiments the symptoms which follow the administration of tetanus toxin are entirely similar to those resulting from infection with the tetanus bacilli. In man, as certain muscle groups are predilectively affected, the order in which the symptoms develop is not so regular as in animal experiments, in which three stages may be differentiated:

1. Localized tetanus, a tonic stiffness of the muscles, which in most species of animals commences in the muscles in the neighborhood of the point of infection or injection.

2. A stage in which the muscles in the neighborhood of those first affected are successively involved.

3. A stage with general reflexly excitable convulsions, essentially resembling the convulsions caused by strychnine.

In animals the first symptoms occur after an incubation period ranging from 8 hours up to a number of days.

The effects of tetanus toxin differ from those of strychnine chiefly in the *long period of incubation* and in the occurrence of tonic muscular rigidity, and particularly in the occurrence of a *localized tetanus.*

The manner in which tetanus develops at first suggested that it was due to a pathologically augmented excitability of some elements in the periphery, but the incorrectness of this view is shown by the fact that curarization or section of the nerves for a time absolutely prevents the local contractures. These have been explained by the peculiar fashion in which this toxin is distributed throughout the body, *H. Meyer* and *Ransom* having shown that this toxin possesses a peculiar affinity for nervous substances, and is transported to the central nervous system exclusively through the peripheral nerve-endings and not at all through the blood. This transportation via the nerves explains the fact that in animals the localized tetanus spreads from the muscles innervated by one spinal segment to those innervated by the neighboring segments.

When introduced into the stomach, tetanus toxin produces no poisonous effects, partly because it is absorbed with difficulty but chiefly because it is rapidly rendered innocuous by the digestive juices, especially by the combined action of bile and pancreatic juice (*Ransom, Carriere, Nencki*). After intravenous injection it disappears from the blood in a few minutes (*Decroly*), and after subcutaneous injection it is so quickly absorbed that rats in which it has been injected into the tail can no longer be saved by amputating the tail at the end of two or three hours, showing that the toxin must therefore be rapidly removed from the point of infection although the symptoms do not appear for a long time. By biological methods, toxin may be demonstrated in the peripheral nerves at the point of injection, it being present in considerable amounts in the sciatic nerve 1½ hours after injection into the leg, although at this time none can be demonstrated in the blood, muscles, or fat (*H. Meyer u. Ransom, Marie*). As this elective absorption by the nerve-trunks occurs only when the axis-cylinder is intact, being greatly delayed by section and entirely prevented by degeneration, it is probable that the nerve-fibrils themselves and not the lymphatics of the nerves are the path by which the toxin reaches the central nervous system.

From the above it appears that, as a result of its great affinity for nervous tissues, tetanus toxin is first absorbed by the intramuscular

nerve-endings at the point of injection or at the point where it is manufactured. It is then transported by these peripheral nerves to the corresponding segment of the cord, from which it then spreads to the neighboring segments, at first to those on the injected side. Progressively other portions of the spinal cord become affected until, in the final stage, general muscular rigidity and increased reflex excitability develop.

Although a portion of the tetanus toxin always passes into the lymph and the blood, it cannot pass from these fluids directly into the spinal cord, but must be absorbed by the terminal organs of other motor nerves, through which it then may travel to the nervous centres.

Under experimental conditions, and also often under clinical conditions, the absorption in the peripheral nerves in the region of the injection or production of the toxin preponderates, and consequently cutting the nerve—for example, when the toxin is injected into a leg section of the sciatic—will protect the animal from ordinarily lethal doses. *Hans Meyer* was able definitely to prove that this toxin travelled to the centres in the nerves, by experiments in which he was able to block the path for the absorption of the toxin by previously injecting antitoxin into the nerves. Under these conditions it is detoxicated by the antitoxin as it travels along the nerves, so that ordinarily lethal doses produce no effects.

It is this absorption of the tetanus toxin by the nervous tissues which determines the limits of the curative powers of the antitoxin. *As the central nervous system and the peripheral nerves do not absorb the antitoxin from the blood,* even a very large amount of antitoxin in the blood will not prevent animals from fatal poisoning, if the toxin be injected directly into a nerve-trunk, for *the antitoxin can reach and detoxicate only that portion of the tetanus which has not yet been absorbed at the point of injection or production and such of it which although absorbed into the blood has not yet been absorbed by the nerve-endings.* This is the reason why, although the prophylactic effect of subcutaneously or intravenously injected antitoxin is certain, its curative effect is very slight. *It can cure only in case a lethal dose has not already been absorbed by the nerves before the antitoxin is injected,* and consequently its effects are determined by the period which has elapsed between the administration of the toxin and that of the antitoxin. The same amount of antitoxin which, when injected with a many times lethal dose of toxin, certainly protects the experimental animals, fails to do this if it be administered a few moments later than the toxin, 40 times the amount of antitoxin being necessary at the end of one hour, while after the lapse of 5 hours a dose 600 times as large is ineffectual (*Dönitz*). If a dangerously large amount of toxin has already been absorbed into the peripheral nerves, the prevention of the invasion of the centres by the toxin may be hoped for only if the antitoxin be directly injected into the nerves in the neigh-

borhood of the injection or site of infection. While cures have been obtained in a number of desperate cases by using the antitoxin in this fashion, once the centres have been attacked by the toxin, subcutaneous or intravenous injection of even very large amounts of antitoxin is almost invariably ineffectual.

In accordance with these experimental results, clinical experience has also shown that, when once the symptoms of tetanus have appeared, it is no longer possible to secure a cure even by enormous doses of antitoxin. On the other hand, the certain prophylactic effect of tetanus serum is explained by the mass action of the antitoxin in the blood and fluids of the body, as a result of which the toxin is kept from combining with the nervous tissues.

The **long period of incubation** for tetanus has been explained by the recognition of the manner in which the toxin reaches the central nervous system through the peripheral nerve, and its length has been shown to depend almost entirely on the length of the nerve path which must be traversed before reaching the centres. Consequently, in larger animals the incubation period is much longer than in smaller ones. However, even when the toxin is introduced directly into the spinal cord, some time must elapse before symptoms appear. This time is evidently necessary for the completion of the reaction between the poison and the susceptible elements of the cord, for, like other ferment reactions, many toxic reactions also proceed but slowly. A certain temperature has also been shown to be necessary for this reaction. Thus, bats when kept sleeping at low temperatures manifest a very high resistance to tetanus toxin (*Meyer u. Halsey*), and in cold-blooded animals tetanus toxin under ordinary conditions remains ineffective. However, as shown by *Courmont* and *Doyon*, tetanus develops even in frogs after a certain latent period if they be kept in water at a temperature of 32° C. *Morgenroth's* experiments, in which frogs did not develop tetanus when kept at low temperatures but quickly did so after they had been brought into warmer water even a long time after the toxin had been injected, show that the toxin reaches the central nervous system at ordinary temperatures and that the high temperature is necessary only that the toxin may become active in the centres.

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DIPHTHERIA

In general similar conditions influence the actions of the antitoxin in this disease, but the manifold actions of the diphtheria toxin furnish more favorable opportunities for this drug to act than is the case with tetanus.

This toxin also is ineffective when introduced into the stomach. When absorbed into the blood, its effects correspond in general to the general effects produced by the bacteria, though in this disease we

are probably not dealing with a single poison but with a mixture of several different ones. They affect primarily the tissues with which they first come in contact, and consequently clinically they, as a rule, first cause a diphtheritic inflammation of the mucous membranes, with the formation of a membrane. When distributed throughout the body, these toxins act on many different tissues, as is evidenced by the toxic decomposition of the proteids, the alteration of metabolism, and the character of the post-mortem findings in different organs, particularly the hemorrhages and hyperæmia of the suprarenals. The lethal effects are due chiefly to a typical depression of all the nervous centres. In experiments on animals, there are also late developing paralyses of the nerves in the neighborhood of the point of infection, which in their nature correspond to the postdiphtheritic paralyses observed in man.

This toxin disappears very rapidly from the blood, for, when it has been injected intravenously, blood infused into a second animal exhibits toxic properties only if transfused within the first 4–7 minutes. In spite of this, however, symptoms of poisoning become manifest only after many hours, even after the administration of many times lethal doses. In such case the experimental animals lose their power of maintaining their normal positions and become paralyzed, while, after a temporary rise, the temperature falls progressively, the reflexes disappear, and all functions of the central nervous system fail, death occurring as a result of paralysis of the respiration.

During the development of the poisoning the blood-pressure sinks in a stair-like fashion, and the heart, which at the beginning of this fall was still beating powerfully, beats more and more weakly, so that after a time cardiac death occurs, even if artificial respiration be carried on. It has been shown that these effects on the circulation are at the start chiefly due to central vasomotor depression, but that in the final stages this is accompanied by a direct toxic action on the cardiac muscle.

It has been shown by *Meyer* and *Ransom* that this toxin also may reach the centres via the peripheral nerves, for, when injected directly into the nerve-trunks, it causes a paralysis of the corresponding centres more rapidly and in smaller doses than when injected subcutaneously. Moreover, even if the wound at the point of injection into the nerves be bathed with antitoxin, or if large quantities of antitoxin be administered intravenously prior to the intraneural injection of the toxin, the local paralysis still develops. It consequently is apparent that it is quite as difficult for the diphtheria antitoxin as it is for the tetanus antitoxin to combine with the toxins, once they have been absorbed into the nerves. In any case, even if the antitoxin is able to penetrate into the central nervous system, it can render harmless such toxin as has already combined with nervous tissues only if it follows it there very quickly. Two hours after the injection of toxin ten times as large doses of antitoxin are necessary to secure the curative effects as are necessary within the first hour (*Berghaus, Marx*).

From the above it would appear that the effect of the diphtheria serum is due only to its power of protecting against the further absorption of new toxin from the points at which it is produced, and not to its possessing any true curative action. This is in accordance with the

clinical experience that, if severe general symptoms of depression of the centres, such as are seen in very virulent infections, have already developed, these cannot always be caused to disappear by the administration of serum. The often astonishing changes in the symptoms which, in less severe infections, usually follow the administration of antitoxin, particularly when the serum is used early, may be explained on the assumption that new toxin can no longer reach the central nervous system, and that the effects of that which has already been combined there can still be overcome by the cells affected.

However, more recent experiments (*F. Meyer*) show that it is still possible to secure a cure by the intravenous injection of very large doses of serum even 6–8 hours after the injection of the toxin, and consequently it is not impossible that the antitoxin by a mass action may attract to itself toxin which has already combined with the nervous centres. On the other hand, this is contradicted by the experience of most observers that the postdiphtheritic paralyses are not influenced by the serum treatment. Recently, however, favorable results have been claimed from the use of very large doses of serum in cases of postdiphtheritic paralysis (*Comby*).

It would therefore appear to be certainly proven only that the antitoxin protects the nervous system and other cells against further absorption of the toxins. Consequently the earliest possible administration of the antitoxin serum is of the utmost importance. Intravenous administration permits the antitoxin to become effective at once, but when administered subcutaneously the serum is absorbed only very slowly (*Morgenroth*). As the intravenous administration apparently produces more pronounced side effects than the subcutaneous injection (*Tachau*), it is perhaps of practical importance that the antitoxin is absorbed decidedly more rapidly when injected intramuscularly than when injected subcutaneously (*Morgenroth*).

The curative effects of antidiphtheritic serum are due to its power not only of protecting the nervous system from further absorption of the toxins but also of neutralizing them in the tissues where the bacilli are multiplying and manufacturing their toxins. These bacilli cause their local effects, such as the formation of membranes, with the aid of their toxins, which cause the damage to the neighboring tissues, as a result of which a favorable culture-medium is prepared for the further multiplication of the bacilli. As the antitoxin neutralizes the toxins in the tissues, the bacilli are deprived of these weapons, and in this fashion is explained its favorable action on the local infection, which is usually rapidly checked by the serum injection, so that, under the influence of the natural curative powers of the body, it promptly clears up. This prevention of the multiplication of the bacilli and of the manufacture of their toxins, then, secondarily aids in bringing about the disappearance of the nervous symptoms, the fever, etc., just as is the case when diphtheria is treated locally by caustic agents as advised by *Loeffler*.

The strength of the antidiphtheritic serum is, like that of other sera, expressed in immunity units, a unit being that amount of serum which in vitro will detoxicate for guinea-pigs a certain amount of standard toxin. According to the German Pharmacopœia, diphtheria serum, which may be preserved by the addition of phenol or creosol, must contain at least 300 immunity units per cubic centimetre. Sera of high potency contain over 500 such units per cubic centimetre. As a rule, 1000–6000 units should be injected, but in severe cases much larger doses should be given. For prophylactic treatment 500 units are, as a rule, sufficient. A dried antitoxin is also obtainable, which contains no antiseptics and must contain at least 5000 immunity units per gramme.

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BACTERIOLYSINS

When, instead of the soluble metabolic products of bacteria, attenuated or killed bacteria are used to produce immunity, the immune sera acquire the power of acting specifically on the bacteria in question. In this fashion it is possible to obtain bacteriolytic sera, as was first shown by *Pfeiffer* for the cholera vibriones.

Guinea-pigs injected with a lethal quantity of these vibriones die with symptoms similar to those of the algid stage of cholera, and very active vibriones are found in the peripheral cavities. If, however, such animals be injected with a sufficient dose of an immune serum obtained from another animal, rendered immune by the injection of non-lethal doses of these bacteria, they do not die, and their peritoneal fluid contains vibriones which are altered in their form and in their behavior to staining agents, and it is possible actually to see "how their bodies pass into solution in this exudate."

The mechanism of this phenomenon has been explained by experiments in vitro (*Metschnikoff*) as follows: Bacteriolysis occurs in vitro only when fresh immune serum is brought in contact with the bacteria, while such serum loses its specific powers when kept for a long time or when heated to 60° C., but regains it when the fresh serum of normal adults is added. This indicates that bacteriolysis results from the combined action of two substances, one of which is present in the normal serum of non-immunized animals, but is very unstable. On the other hand, the specific component of the bacteriolysin, which is present only in the serum of the immunized animals, is more stabile and resistant to heating.

Of **bactericidal sera** we have thus far antistreptococcal, antimeningococcal, antipneumococcal, antityphoid, and anticholeraic sera and many others, but their practical value is still *sub judice*.

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HÆMOLYSIS

The studies of bacteriolysis have led to the clearing up of another biologically important phenomenon, that of hæmolysis. Just as specific antigens, the bacteriolysins, are formed in the body after injection with the antigens of the bacterial bodies, so also the sera of animals injected with other heterologous blood-cells acquire the power of acting specifically on and of dissolving these cells. Thus, the injection of heterologous blood-cells causes the production of hæmolysins. For example, if a guinea-pig be injected with a rabbit's blood, its serum, which normally does not hæmolyze rabbit's blood-cells, becomes hæmolytic for these cells. Such a hæmolytic serum becomes ineffective when heated to 55°–60°, but may be reactivated by the addition of fresh normal rabbit or guinea-pig serum. As was first recognized by *Bordet,* hæmolysis also is due to the combined action of a thermolabile normal constituent of the blood and a thermostable antibody, whose formation results from the injection of a heterogeneous blood. Normally the serum of many species of animals is hæmolytic for certain heterologous bloods, so that without any preparatory treatment they hæmolyze them.

Hæmolysis results from the hæmolysin attracting to itself the antigen contained in the red cells and thus causing the destruction of their structure. It goes without saying that hæmolysis may also result from pharmacological actions of a very different sort, if only these actions are exerted upon integral constituents of the cell body. Examples of this are the hæmolysis produced by substances which dissolve the lipoids which form a portion of the body of the blood-corpuscles,—for example, that caused by saponin or by chloroform, ether, etc. The hæmolysis produced by hypotonic salt solutions, which cause destruction of the cells as a result of the inhibition of water, may also be mentioned.

The thermolabile substance present in the serum, the coöperation of which is essential for hæmolysis, is probably derived from the leucocytes, being either secreted by them or set free when they die. Thus far there is no uniformity in the conceptions of the manner in which these two substances act together in bacteriolysis and hæmolysis. According to *Bordet's* views, both substances act directly on the cells, but the substance present in normal serum, named by him cytase, can produce lysis only if the specific substance formed during immunization, named by him "substance sensibilitrice," has acted on the cells in a manner comparable to that in which mordants prepare fabrics for dye-stuffs.

Ehrlich, on the other hand, was able to show that the stable specific substances, but not the thermolabile ones, the complement, may be made to combine with susceptible red cells and thus be removed from the serum. He consequently assumes that the substance formed during immunization, named by *Pfeiffer* the immune substance and by *Ehrlich* amboceptor, combines with the blood-cells but by itself cannot produce lysis. It is only when it combines with the complement that a substance is formed which combines with the cells and dissolves them.

More recently *Arrhenius* has explained the combined action of these two substances on the assumption that the effective compound formed by the immune body and the complement is not formed in the serum, or else is not stable there, but that it is formed only in the blood-cell when both substances are present.

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Agglutinins.—As a general thing antibacterial immune sera produce a second specific effect on the corresponding bacteria, which consists in agglutinating them. These agglutinins, which were discovered by *Gruber* and *Durham*, are of great practical importance, particularly as a means of diagnosing typhoid (Widal reaction).

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Precipitins.—Another property of many antibacterial immune sera is their power of precipitating substances obtained from dead bacteria of the species used for immunization (*Kraus*). The substances responsible for this precipitation are known as precipitins, and are always formed when heterologous proteid reaches the blood. Thus precipitins for serum albumin, lactalbumin, etc., may be formed. As sera thus obtained always give the precipitate or cause precipitation in the highest dilutions only with the proteid (the precipitinogen) used in the preparatory treatment, and as the reaction grows weaker the more distant the relationship between the tested proteid and the precipitinogen, this biological reaction has acquired great importance as the most delicate means of distinguishing between different proteids, —for example, in the differentiation between human and animal blood.

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Cytotoxins.—Specific serum may be prepared not only against blood-cells and bacteria but also for all possible kinds of cells. Thus, by preparatory treatment with spermatozoa *Landsteiner* has obtained a serum which paralyzes their movements, and *v. Dungern* a specific serum for ciliated epithelium. These cytotoxins are also in a certain sense specific, being always most toxic to those cells which were used in the preparation of the serum. These investigations are mentioned here because it appears entirely possible and probable that cytotoxic sera may be used to cause specific destruction of or damage to certain cells, as, for example, those of neoplasms.

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CHAPTER XVIII

FACTORS INFLUENCING PHARMACOLOGICAL REACTIONS

Solubility.—The old axiom "Corpora non agunt nisi soluta" should be corrected by the addition of " seu solibilia." For instance, undissolved zinc reacts with sulphuric acid in the presence of water and is dissolved in it, but gold, being insoluble, is inactive. This law holds true in all pharmacological reactions, and, if a substance or compound is completely insoluble in the body, as is the case with barium sulphate, or paraffin, it produces no pharmacological effects, but, if it is soluble to start with or if it becomes so as a result of interaction with the tissues, as is the case with sulphur, it can produce such reactions.

Most of the chemical antidotes act by transforming the poisons in the stomach and intestines into insoluble—or at least poorly and slowly soluble—compounds, thus preventing or at least retarding their absorption and their toxic actions.

Adequate Amount.—While solubility is the first essential for a pharmacological effect, the second one is that a sufficient quantity of the drug shall come in contact with the tissues or organs on which it exerts its actions.

The receptive organs of the nerves of taste and smell react to immeasurably small quantities of active substances, and many other cells act to equally small amounts of adequate physiological stimulants. As an example of this the reader is reminded of the chemically scarcely recognizable and still efficient epinephrin content of the arterial blood. Moreover, certain other substances may, under certain conditions, prove toxic in almost immeasurably small amounts, as is the case with those minute traces of copper which are present in water distilled from a copper vessel, and which exert a harmful action on certain vegetable or animal cells introduced therein (p. 563).

In all of these and in all analogous cases where extremely small quantities of drugs exert a physiological activity, it has been possible experimentally to determine the lower limits and the conditions for such activity. They have nothing whatever to do with the claimed effects of homœopathic dilutions of drugs. The claims made by homœopathy are based on no experimental tests, but only on uncritical and, from their very nature, improbable hypotheses.

DIRECT LOCAL ACTIONS will, it is clear, be influenced by the amount applied and, in the case of substances already in solution, the concentrations employed.

Power of penetration into the deeper tissues is also of special importance for any action elsewhere than on the very surface of the body. Caustic substances, which destroy the tissues, penetrate with difficulty if they form a firm and insoluble eschar, but more readily if the compounds formed are soft or fluid (see Caustics, p. 491). In general, lipoid-soluble substances penetrate more readily than lipoid-

insoluble ones, and of these latter the readily diffusible more readily than those which diffuse with difficulty. This last rule, it is clear, holds good for the

Absorption of drugs from the circulating blood by cells lying at a distance from the original point of absorption.

The concentration of a drug in the blood, which determines its quantitative distribution in the various cells and organs, depends on the relative rapidity of its absorption and of its elimination or destruction. A drug reaches the circulation most rapidly and to the full amount of the dose administered when it is injected intravenously—in the case of gases when it is inhaled—and almost as rapidly when injected intramuscularly; but decidedly more slowly, and almost never in its entire amount, when it is injected into the subcutaneous tissues, for a portion of it is absorbed and more or less tenaciously retained by them. Drugs enter the blood most slowly and least completely through the mucous membranes, and of these the mucous membranes of the stomach and of the bladder are almost impermeable for substances not soluble in fats. When absorbed from the intestines, drugs first pass into the liver, where they meet with a new barrier, many of them being transformed chemically by this organ, while others are absorbed and retained by it, at any rate for a time.

If the elimination through the stomach, intestines, or lungs, or if the distribution of the drug keep pace with its absorption, its concentration in the blood can never become high, and in the case of many substances, such as curare, if they be administered orally, the concentration in the blood never attains an adequate or threshold value. In case the normal active elimination be pathologically diminished, for example by renal insufficiency, it is possible that an unexpectedly high concentration of the drug in the blood may be attained so that a correspondingly pronounced pharmacological or toxic action results.

Distribution.—With a certain concentration of the drug in the blood, however, it (the drug) is by no means equally distributed between all the organs and cells, but, according to their particular physical or chemical affinity for the drug, it is absorbed by them in different amounts and with varying rapidity. Consequently the final distribution of a drug throughout the body depends also on the rate at which it enters into the various tissue fluids. If the whole quantity enters these at one time, the more avid cell *A* will, in comparison with the less avid cell *B*, attract to itself relatively more of the drug than will be the case when the drug enters these fluids only gradually and consequently circulates around in these fluids for a longer time but in higher dilution. If *A* be not only the more avid but also the specifically susceptible cell, and *B* the less avid and relatively insusceptible cell, the pharmacological effect is more pronounced when the whole dose is given at once; but, if the more avid cell be the less susceptible

one, then small, rapidly repeated doses will be the most effective. While it is not possible to predict for every drug how it will behave in this respect, it is possible to determine this empirically for any given one (*Beinaschewitz*).

Except in the case of the locally acting caustics and irritants, the quantity of the drug which actually acts on the specifically susceptible cells, as a rule, forms only an immeasurably small portion of the dose administered. After absorption a drug is distributed by the blood and lymph throughout the whole body, and, according to its physicochemical properties, is retained and stored up by cells of the most different sorts, either mechanically or by capillary adhesion or by entering into solution or chemical combination with the cellular constituents. Cumulation—that is to say, the absorption and retention of relatively large amounts of the drug by certain cells and cell complexes—renders possible the elective action of even extremely small doses. For example, 1 mg. of digitoxin distributed throughout a body weighing 70 kilos gives a dilution of one to 70 million, a concentration which is far from high enough to exert any appreciable action on the cardiac muscle, were it not for the fact that this poison is absorbed and retained by the cardiac muscle more than by any other cells, and consequently may attain in it an adequate concentration, just as copper salts in an extremely dilute solution (1 mg. in 100 l.) are absorbed and accumulated by algæ in far greater concentration (*Devoux*).

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Relationship between the Size of the Dose and the Intensity of the Pharmacological Action.—While the absorption and the sufficient storing up of a drug in certain cells and organs are naturally a necessary preliminary condition for its elective pharmacological action thereon, it can by no means be used as a measure therefor, for many cells may accumulate a substance in considerable amounts without being harmed or functionally disturbed (*Straub*). Examples of this are the intra-vital staining methods used in histology and the forensically important accumulation of many poisons in the liver, kidney, spinal marrow, etc.

The amount of the drug which finally becomes effective determines the actual degree of the pharmacological action, but this amount and the effect produced are by no means directly proportional, for so long as it remains below a certain amount, the threshold value, no appreciable effect at all is produced, for very slight chemical disturbances are borne by living cells without appreciable alterations of their functions, just as they support the daily and hourly variations of osmotic tension, of temperature, and of other factors in their normal environ-

ment. Consequently the ineffective or just effective doses must be subtracted from the different doses administered in order to determine the true ratio between them.

If, as is always necessary in the case of medicinal administration, that portion of the drug which is retained in other organs, and which does not reach the insusceptible organs at all, be also included in the "threshold dose," the difference becomes still greater.

For example, if for a normal adult the empiric threshold dose of digitoxin be about 0.9 mg.,—that is, if this be the dose which produces a hardly appreciable effect,—the amounts of digitoxin which actually come into action when 1 mg. and when 2 mg. are administered may be stated to be in the proportion (1.0 minus 0.9) to (2.0 minus 0.9), *i.e.*, 0.1 to 1.1 = 1 to 11. Consequently, while the pharmacological effect of 1.0 mg. may be just appreciable, the dose of 2.0 mg., which is apparently only twice as large, may be unexpectedly severe and perhaps dangerous. This example is not a hypothetical one, but is the result of experiments made by *Koppe* on himself.

Unfortunately, we have no methods by which the intensity of pharmacological actions may be directly measured except in the case of certain blood poisons, in which the intensity of action may be estimated by the extent to which the red cells lose their coloring matter.*

The final amount of hæmolysis caused in like suspensions of blood-cells by different quantities of a hæmolytic agent expresses, in percentages, the functional relationship between the amount of the hæmolytic agent and the intensity of its action.

Further, the rapidity with which a certain determinable effect (for example, the cessation of respiration in fish or the death of bacteria) occurs after a certain dosage may serve as an indirect measure of its activity. In such case the degree of activity is the reciprocal of the rapidity with which the action is produced. Using such methods, it has been shown that, as a rule, the rapidity with which toxic effects are produced increases much more rapidly than do the corresponding doses, calculated after subtraction of the threshold dose.

In Fig. 62 the curve represents the intensity of the hæmolytic action, and in Fig. 63 the unbroken curve represents the time required for the various concentrations of ether to narcotize small fishes, and the broken curve, which is the reciprocal of the time curve, represents the intensity of the narcotizing action. Both of these curves, the one indicating the percentage of hæmoglobin dissolved

* This method, however, assumes that with partial hæmolysis each red blood-cell gives up a corresponding portion of its hæmoglobin,—that is, is partially poisoned. However, up to the present it is uncertain whether this is actually the case, or whether in the partial hæmolysis of a given number of red cells a certain portion of them are completely hæmolyzed while the rest retain their normal quantity of coloring matter. As a general thing, this last is assumed to be the case, although, in view of the regular curves of hæmolysis obtained in such experiments, this is hard to understand. According to unpublished experiments of *Handowski*, partial hæmolysis is the expression of the different resisting powers of the different blood-corpuscles in a certain quantity of blood, and it appears that the youngest blood-cells are the more resistant to hæmolytic sera and those hæmolysins which act on the lipoids.

out of a given number of erythrocytes by increasing amounts of saponin and the other the intensity of the narcotic action of increasing amounts of ether, show the rapid augmentation of the toxic action. The efficiency of disinfectants increases just as rapidly in proportion to the increase of their concentration, the time needed for the killing of bacteria being indirectly proportional to the efficiency of different concentrations (*Paul, Birstein, u. Reuss*).

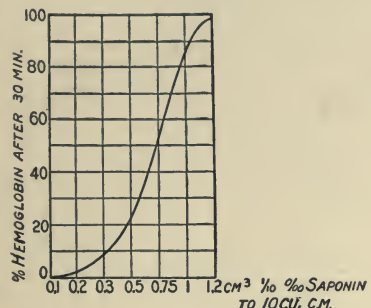

FIG. 62.

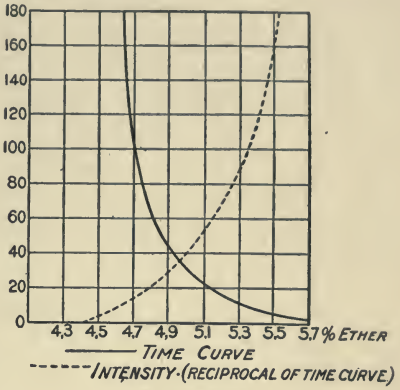

FIG. 63.

This means that cells acted upon and to some extent affected by a certain amount of a toxic substance, or certain portions of them not yet affected and still functioning normally, become less and less resistant and more and more susceptible to increasing amounts of the same substance, until finally the smallest increase is sufficient to produce the maximum effect. This is apparently almost the converse of the ratio between the intensity of perception and increasing stimuli as expressed in the law of *Weber* and *Fechner*. Fig. 64 expresses this contrast graphically.

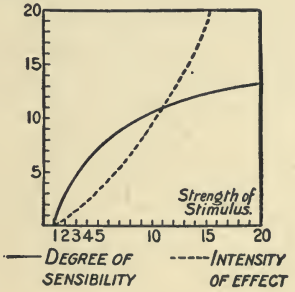

FIG. 64.

In many cases the effect produced by very small doses is the direct opposite of that produced by larger ones, the smaller doses stimulating certain vital phenomena while larger ones inhibit them, just as moderate heating stimulates, while overheating first narcotizes and finally kills living cells (*H. Meyer*). In animal pharmacology we meet with

this reversal of the effect in the case of the narcotics of the central and peripheral nervous system, in connection with many central excitants,—for example, strychnine, HCN, and H_2S,—and with many so-called alternatives,—for example, arsenic, phosphorus, etc. Vegetable pharmacology also offers many similar examples,—for instance, the activity of yeasts may be quite generally augmented by minimal amounts of different inorganic substances which in large amounts depress or paralyze them (*Schulz*), and the same has long been known of the effects of such substances on bacteria and moulds.

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Pharmacological Actions Influenced by the Functional Condition of the Organs.—Another much larger and more important group of factors affecting the pharmacological action of various drugs and the whole picture produced by them is found in the composition and structure and the momentary conditions of those organs and cells which are directly acted upon by the drugs in question. In this fashion differences, which are otherwise unrecognizable, may betray themselves by very striking differences in pharmacological reactions, and these, in even the most simple of experiments, may lead to apparently contradictory results.

A well-known example of this is the effect of caffeine in frogs, in which certain earlier investigators observed only a reflex tetanus similar to that produced by strychnine, while others noted only a muscular rigor which was quite independent of any action on the spinal cord. Consequently their explanations of the actions of caffeine were entirely different. One group of these investigators, however, had used only Rana esculenta, while the others had used R. temporaria, and later investigations showed that in these two species of frogs both of these pharmacological actions were produced, but that in one species the augmentation of reflex excitability and in the other the muscular rigor was more readily induced. Consequently, when the pharmacological action developed rapidly, only one of these effects was apparent and concealed the other (*Schmiedeberg*).

Such differences in susceptibility are observed not only between the muscles of related or entirely unrelated species, but also between the muscles of a single individual. Thus, the more excitable muscles, which are more generally active in daily life, react to pharmacological agents more rapidly and more decidedly than the more sluggish and less used ones. Thus, in birds of flight the leg muscles are less susceptible than the much used wing muscles, while the contrary is true in those birds which do not fly; and in chronic lead poisoning the muscles of the hand and forearm, which are those most used in ordinary labor, are the first to be affected by paralysis (*Teleky*). Even greater differences in the effect of drugs may be observed in muscles

with normal tone and those in which the tone is pathologically augmented or depressed. Thus, the gravid uterus, whose muscle-fibres are more stretched than those of the non-gravid organ and which consequently are more susceptible to contractile stimuli, ordinarily contract when the mixed hypogastric nerve, which contains both exciting and inhibitory fibres, is stimulated, while the opposite effect is produced in the non-gravid organ. Pilocarpine and epinephrin, like the electric stimulation of this nerve, in the one condition cause the uterus to contract and in the other to relax (*Cushny*). What has been stated above for the muscle-cells holds good also for all the other cells of the organism.

Generally one may assume that all living cells will show the thus far inexplicable tendency to maintain a normal functional mean of activity or position, and that they will of their own accord return to it if forced to depart from this mean in one direction or the other. It is this self-regulating inherited tendency of cells which is responsible for the permanence of the individual and of the species, and which is the essential cause of the vis medicatrix naturæ. A very simple and at the same time characteristic and instructive example of this is the behavior of the tissue cells in the presence of changing osmotic tension. If the surviving liver be transfused with hypotonic saline solution, it swells up slowly as a result of the swelling of the individual cells, but if an isotonic solution be then transfused it rapidly regains its normal size and condition. In a similar fashion, under the influence of hypertonic solutions, it shrinks but slowly, and regains its normal condition very rapidly when isotonic solutions are transfused (*Demoor*).

It would thus appear that in living cells osmotic reactions back toward the normal are much more readily induced than those in the opposite direction. Much the same holds good for the varying conditions of tension in contractile elements, the state of excitation or tone of nerve centres, etc. In this connection the reader is reminded of the powerful action of the antipyretics on the pathologically excited heat centres (p. 466), and of the power of digitalis to regulate the irregularly beating heart (p. 296).

It must not be forgotten, however, that in the case of many organs and functions the conditions are not so simple as in the above-mentioned examples; for normally most of these are continually under the influence of a double antagonistic innervation, through which they receive both exciting and inhibiting stimuli, either through nervous stimulation or the action of chemical substances, such as the hormones. Thus, the intestinal musculature receives exciting impulses through the vagus and inhibiting ones through the sympathetic; consequently, if the intestine be completely relaxed, solely because it is receiving no exciting stimuli through the vagus, any agent which stimulates the vagus produces a marked effect upon it and readily

causes a contraction and to a greater degree than if the intestine had originally been in a state of moderate contraction. On the other hand, if the original relaxation had been due to powerful inhibition through the sympathetic, this would oppose the action of the agent exciting the vagus, and consequently the effect would be slighter than if the intestine had been in a state of ordinary repose.

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ANTAGONISM.—This physiologically antagonistic nervous mechanism of all the vegetative organs, the unstriped muscles, the glands, and the circulatory organs, must consequently often modify the actions of those drugs which act on this system, and be the cause and the explanation of the reciprocal antagonism between those pharmacological agents which excite the activity of the two portions of this antagonistic nervous mechanism.

The antagonistic effects of small and large doses of the same drug may also depend on this physiologically antagonistic innervation. Thus, according to *Schwartz*, small doses of choline excite the inhibiting centres for the pancreatic secretion, while large doses stimulate the secretory nervous organs lying in the gland itself. *Wertheimer* and *Lepage* state that just the opposite is true for atropine.

Little is actually known, and still less is understood, of the antagonistic effects produced in the various organs by the internal secretions, which may be looked upon as physiologically formed pharmacological agents. Among these mention may be made of the partial antagonism between choline and epinephrin (see pp. 164, 188, 189). In other cases, such as that of the probably antagonistic action of epinephrin and the pancreas hormone on the liver-cells (see pp. 171, 419), we are entirely in the dark as to how they act, nor can this antagonism be explained in the above-mentioned manner. When we endeavor to explain the antagonistic actions of the thyroid hormones and those of the hypophysis and of the reproductive glands, we are still more at a loss.

There is no particular difficulty in understanding the antagonism between various drugs and poisons when this depends on the antagonistic innervation of certain organs. Thus, if a drug stimulates the vasodilators it is clear that it must oppose the action of another which stimulates the vasoconstrictors.

Much more difficult to understand, however, is an antagonism in which one drug overcomes the effect produced by another one in the same cell or functional element without the aid of any antagonistic physiological mechanism. Here it is necessary to differentiate between

two fundamentally different methods by which such results may be obtained,—namely, by distoxication and by true physiological antagonism.

(*a*) *Distoxication.*—When one substance chemically changes or combines with another,—that is, satisfies its specifically active affinity,—it appears to act antagonistically. Such an action we speak of as a chemical distoxication, examples of which are the distoxication of cyanides and of nitrils by hyposulphites.

Hydrocyanic acid and the nitrils, for example malonitril, are readily transformed by active sulphur into the less toxic sulphocyanides, and consequently it is possible, by subcutaneous or, better, by intravenous injection of a solution of hyposulphite, to rescue animals which have received lethal doses of a cyanide or a nitril and which are already in the death struggle. On account of the extraordinary rapidity with which the respiratory centre is paralyzed in cyanide poisoning, the antidote in such cases must immediately follow the poison, or artificial respiration must be performed for some minutes, in order to overcome the effects of this toxic action. As the nitrils produce their effects much more slowly, their distoxication can be accomplished after the lapse of a considerably longer period.

In this case the antidote penetrates into the already poisoned cells or into their immediate neighborhood, and destroys the poison absorbed by them, a fact which is of decisive importance for its efficiency.

Examples of distoxication as a result of chemical combination are furnished by the distoxication of free acids by alkaline carbonates, that of oxalates by lime salts (*Januschke*), and that of the saponins (*Ransom*) and of the crotalus toxin (*Fühner*) by cholesterin.

When the combination formed by the poison and the protoplasm, or more correctly the reacting constituent thereof, is reversible with difficulty or not at all (for instance, on account of its complete insolubility), it is quite clear that even an adequate antidote, which is able to combine with the poison, cannot reverse the toxic reaction. However, in such case it may be possible to repair the protoplasm by replacing such of its constituents as have combined with the toxic agent. This is actually what occurs in the antagonistic action of lime salts in oxalate poisoning. When, on the other hand, the toxic reaction is readily reversible, as for example in chloral or chloroform poisoning, a substance which possesses an avidity for the toxic substance equal to or greater than that of the cell constituents can attract the toxic substance to itself and thus overcome the poisoning of the cell. Thus, according to *Nerking,* it is possible to lessen or overcome a deep chloroform narcosis by the intravenous injection of a lecithin emulsion.

(*b*) *True Antagonism.*—The antagonism between atropine and muscarine is the classic example of true physiological antagonism, for these two antagonistically acting drugs have no chemical affinities for and do not react with each other, but produce directly opposite effects upon the same organic elements.

Nasse's studies of the action of poisons on ferments have given

us a knowledge of the simplest type of this kind of antagonism. He found that the activity of the yeast ferment, invertin, was inhibited by KCl and accelerated by NH_4Cl, and that in certain relative proportions these two substances could overcome each other's actions; and that the same was true for the alkaloids quinine and curarin, the first inhibiting, the latter favoring, and the two together, if in proper proportions, leaving unaltered the activity of this ferment. In other words, he found that there was a complete reciprocal antagonism between these substances. Inasmuch as neither potassium chloride nor curare enters into any chemical reaction with ammonium chloride and quinine respectively, we are able to understand their reciprocal antagonism only if we assume the existence in the ferment of a common point of attack for both of the antagonists, which is influenced in opposite directions when it combines with one or the other of these.

A somewhat rough comparison may aid in elucidating this. Sea water possesses a certain conductivity or, in a physiological sense, excitability, which may be increased by the addition of alum or markedly decreased by that of alcohol, for the former is an electrolyte and the latter a non-conductor. Either of these may be removed from the water by the addition of the other, for the alum can be precipitated by the addition of alcohol and conversely the alcohol may be separated from the water by the addition of alum. Consequently, according to the varying proportions of these two substances added, an equilibrium may be established in the sea water with increased, diminished, or unaltered conductivity. An example of a similar phenomenon closely resembling certain vital phenomena is furnished by the action of saline solutions on colloids, the salts of monovalent and bivalent metals inhibiting each other's power of precipitating proteid and, according to their effective amounts, forcing each other out of their sphere of activity. An entirely similar antagonism between the monovalent and polyvalent metallic ions has been demonstrated in connection with the action of saline solutions on living organisms, such as fundulus eggs, and muscles and contractile organs generally.*

These facts compel us to assume for the antagonists in question a similar reversible reaction,—that is, a labile combination of some sort or other with the common substratum of the living cells, in which, according to the preponderance of one or the other of the antagonists, inhibition or excitation of the cell function is more strongly developed. For such a hypothetical phenomenon there actually exists an exactly investigated example in the behavior of oxygen and carbon monoxide in the red cells. Here oxygen is the stimulating or exciting agent and carbon monoxide the inhibiting or depressing one, and, while they do not react with each other, they both possess a similar but quantita-

* In this connection special mention should be made of the reciprocal antagonism between K and Na ions, which, so long as their relative proportion be about 1 to 17, are non-toxic to the fundulus, but which, if this relative proportion be altered appreciably, no longer compensate each other and become toxic (*Loeb*).

tively very different affinity for hæmoglobin, and consequently, according to the relative amounts present, are able to force each other out of their combinations with hæmoglobin. It is for this reason that it is possible, by supplying oxygen freely, to restore to a normal condition blood which is actually saturated with carbon monoxide, provided only that the poisoning has not already persisted so long as to bring about the death of the erythrocytes. Under such conditions, however, the removal of the carbon monoxide takes place slowly and with difficulty, for its affinity to hæmoglobin is 200 times as great as that of oxygen, and consequently the feeble affinity of the oxygen molecules must be compensated for by their number,—that is, by a larger amount and higher concentration. For this reason inhalation of oxygen can by no means always rescue the victims of coal gas poisoning, for the removal of the carbon monoxide requires so long a time that in the interim the brain and the heart may succumb to asphyxia.

In the above we have touched on a question of fundamental importance, the question as to the possibility of an **absolute reciprocal antagonism.** This possibility has been repeatedly denied on the ground that, while it is possible to bring about paralysis in a stimulated organism, it is not possble to bring about stimulation in a paralyzed one, and that the paralyzing poison under all conditions will maintain the upper hand. In a static sense this is correct; but the static condition in a cell poisoning holds good only for the irreversible toxic actions of colloids, toxins, and certain metallic ions, while in almost all other acute poisonings the combination between poison and protoplasm is a dissoluble one, so that the cell may be restored again and the poison washed out from it if it be bathed with blood which has been freed of the poison. If then the indifferent pure blood be replaced by one containing an antagonistic drug,—that is, one possessing a similar affinity for the affected elements of the cells,—the original poison must be forced out from its combinations and the distoxication be accelerated, while at the same time the stimulating antagonistic effect of the antidote will produce its action.

A very instructive example of such an antagonistic rivalry between two substances is furnished by the effect of lime salts in combating the narcotic effects of magnesium salts (*Meltzer* and *Auer*) (see p. 110). In a more general form this reciprocal antagonism between the four cations Ca′, Mg′, Na′, and K′ is more or less clearly evidenced in living organisms, for the tissues apparently can maintain their normal functions, particularly their normal excitability, only when these cations are present in the tissues in their correct relative proportions (*Loeb, Meltzer*). It is probable, also, that the fact that the previously mentioned toxicity for low forms of life, exhibited by the minute amounts of copper present in distilled water, may be abolished by the addition of a small amount of NaCl, is to be explained in a similar fashion (*Bullot, Loeb*).

The reciprocal antagonism between atropine and pilocarpine and muscarine is also to be attributed to similar factors. Here, too, the affinity of one of the toxic agents for the cell protoplasm and perhaps also its power of penetrating into it is greater than that of the other, just as is the case with carbon monoxide and oxygen, and consequently the antagonistic effect may be looked upon as dependent on the relative toxic affinities and the effective quantities and the rates of reactions of the different drugs.

In this view of these phenomena it is assumed that the antagonistic drugs possess a common—that is, exactly the same—seat of action in the organs; but, as a matter of fact, this is absolutely incapable of experimental proof, and can be logically deduced only in those cases where strict reciprocal antagonism has been demonstrated. However, there is another possible explanation for such antagonism,—namely, that the paralyzing drug acts on the cells at a less peripheral point than does the stimulating one. In such case, on the one hand, the paralyzing drug would block the path for the stimuli arriving through the nerves to such a degree that these stimuli would no longer reach the more peripheral elements with sufficient strength to produce excitation, while, on the other hand, as the stimulating drug renders these last-mentioned elements more excitable, it would in turn be able to render them susceptible to previously ineffective stimuli. If the depression or paralysis—that is, the blocking—is so complete that absolutely no stimulating impulses can pass, the stimulating antagonist is ineffective, and consequently in such case one may in a strict sense speak only of a one-sided or pseudo antagonism. This would appear to be the case, for example, with the antagonism between curare and physostigmine, and it is probable that the antagonism between cerebral and spinal stimulants and depressants rests upon a similar basis. For example, morphine narcosis may be partially counteracted by atropine, and atropine excitation by morphine. A similar partial antagonism exists between such narcotic drugs as chloral hydrate and alcohol, and such stimulating ones as caffeine, strychnine, and cocaine.

Probably in all these cases we are never dealing with a complete paralysis but only with a great weakening or obstruction of the conduction of excitation, so that the normal impulses are weakened or retarded on their way to the motor ganglion-cells and consequently are unable to produce in them the essential discharge of nervous energy. The antagonistic stimulating drug may then possibly so lower the threshold for stimuli in the motor neuron or in the interposed switching stations that the abnormally weakened centripetal stimuli are sufficient to bring about the necessary discharge of energy. This conception is supported by the fact that the receptive organs of the spinal reflex arc are always more rapidly and markedly affected by narcotic drugs than are the motor ones, so that the latter may still retain an almost normal excitability and yet remain at rest because they do not receive adequate stimuli from the inhibited receptive tracts.

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IMMUNITY.—Many forms of immunity are based upon chemical distoxication, this being particularly true for immunity to toxins (see p. 547), for, as previously stated (p. 552), the antitoxins, which have been formed in the body, circulate about in the blood and capture, as it were, the toxins which may enter it.

Apparently the antitoxins penetrate only with difficulty or not at all into the pericellular lymph-spaces or the cells themselves, for, if a toxin without entering the circulation be brought in contact with the susceptible cells, it produces its typical effects upon them even in immunized animals whose blood is full of antitoxin (*Meyer, Hume, Ransom, Gley*). Many other poorly diffusing bodies behave in a similar fashion. For example, sodium ferrocyanide solution may be injected into the blood without producing any notable effect, but, if the spinal cord itself has been injured by a small puncture, or cut so that the poisoned cerebrospinal fluid can penetrate to it, violent symptoms of poisoning immediately appear.

Immunity to toxins is consequently practically a humoral one, and, with the exception of congenital insusceptibility, thus far it has not been possible to demonstrate or produce a cellular immunity * except in the case of the immunity of the red cells to eel serum (*Tschistowitsch*).

On the other hand, immunity to all other poisons is almost always cellular, whether it be a natural one or one acquired by habituation.

The immunity of the rabbit to atropine appears to form an exception to the rule, for, according to *Fleischmann*, the serum of rabbits possesses the power of destroying atropine, a property not possessed by the blood of goitrous rabbits, which are quite susceptible to atropine (*Cloëtta*).

Salamanders are very insusceptible to curare, and it has been claimed that this immunity can be transferred to other animals by the injection of salamander blood, but *Heuser* was unable to confirm this.

In many cases we to a certain extent understand the chemical agencies with which the cells render poisons harmless or with which they defend themselves. Thus, the liver-cells neutralize acids with ammonia, which otherwise would be synthetized into urea, and distoxicate numerous poisons by conjugating them with glycuronic and sulphuric acids or by oxidizing or reducing them. These chemical powers of the cells may be very decidedly augmented by exercise; for example, by the administration of increasing doses it is possible to increase the power of conjugating camphor with glycuronic acid (*Schmiedeberg u. Meyer*) or the power of destroying morphine

* Genetically, immunity to toxins is, however, cellular, for the antitoxins are reaction products and cast-off portions of cells.

(*Faust*). By gradually storing up calcium and transforming the soluble fluoride into the insoluble calcium fluoride, yeast cells can accustom themselves to a concentration of ammonium fluoride which at the start would have been very poisonous (*Effront*).

In other cases this chemical cellular immunity has not yet been completely explained. For example, in the above-mentioned habituation to morphine, the insusceptibility of the cerebral cells, which apparently take no part in the destruction of the morphine (*Rübsamen*) and which in spite of this become very insusceptible to this drug, is entirely unexplained, as is also the relative immunity of the morphinist to cocaine (*Chouppe*). Equally unexplained is the great natural immunity of the hedgehog, chicken, and frog to cantharidin, and that of the cardiac muscle of the toad to digitalis-like substances. Surprising but still capable of explanation is the immunity of certain moulds (Penic. glaucum, etc.), which can live in solutions containing from 1 to 2 per cent. of $CuSO_4$, while others (for example, Muc. mucedo) are killed by 0.016 per cent. of this salt, and algæ even by 1 in a billion. In this case the immunity is due to the impermeability of the cell wall of the Penic. glaucum for this salt. [This mould shows the same insusceptibility to Zn and to Hg salts (*Pulst*).]

On the other hand, it goes without saying that toxic substances cannot produce their specific effects in organisms in which the corresponding susceptible organs are either not at all or not sufficiently developed. In animals which have no vomiting centre apomorphine cannot produce emesis, and strychnine cannot cause reflex convulsions in fœtuses and new-born animals, in which the spinal cord is not yet completely developed (*Gusserow*).

Moreover, when the later effects of a toxicological action, such as the secondarily caused death, are alone noted and used as the criterion and measure of immunity, paradoxical results are obtained. In such case frogs would appear very immune to curare, because paralysis of the respiration does not kill them so long as their skin is exposed to the air; and mice would appear relatively immune to CO, for in the presence of a low external temperature they are able to withstand otherwise rapidly fatal amounts of this gas because they cool off rapidly to the surrounding temperature and, like hibernating animals, so lessen their metabolism that they are able to get along with the small amount of oxygen which is still brought to them by the hæmoglobin (*Bock*). Further, the fœtus in utero supports without direct damage long-continued morphine or chloroform poisoning, because it does not use its own respiratory organs, but, when it is born and becomes dependent on its own respiration, it is extremely readily killed by the smallest quantities of morphine or chloroform. This is the explanation of the fact that a deep morphine or chloroform narcosis, induced in the mother a short time before or during the birth, imperils the life of the child, although this is not the case during the pregnancy.

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Synergism.—If the weakening or prevention of the action of one drug by that of another be called antagonism, the one-sided or reciprocal augmentation of such action may be termed synergism (*Fühner*). As this phase of pharmacology has thus far been the subject of comparatively few exact investigations, our knowledge of it is relatively slight.

An increased carbon-dioxide tension in the blood (diminution of the alkaline carbonates in acid intoxication) favors the toxic action of the chlorates on the red blood-cells, perhaps because of an increased liberation of free chloric acid. Another example is furnished by the combined effects of cocaine and epinephrin, *Fröhlich* and *Loewi* having found that doses of cocaine which by themselves produce no appreciable effects very markedly increase the effects of epinephrin on the blood-vessels, the muscles of the bladder, the dilator of the iris, etc. In this case the effects cannot be considered as due to a simple summation of similar pharmacological actions, for they are altogether too great. At present no satisfactory explanation for the above can be given, and for the present we must satisfy ourselves with merely stating that the cocaine produces a sensibilization comparable to the sensibilization of light-sensitive substances or to the action of the mordants in dyeing.

Of much greater practical importance is the synergism of the narcotics,—for example, the combined effects of scopolamine and morphine (see p. 79), of morphine and ether or nitrous oxide, of scopolamine and urethane, of magnesium sulphate and chloroform (*Meltzer, Bürgi*). A similar, or rather an analogous, phenomenon is the very powerful action exerted on the heat-regulating centre by combinatious of certain convulsant poisons and hypnotics (see p. 473).

Such augmentation of pharmacological actions may be determined quantitatively with greater exactness with combinations of hæmolytic substances. Mixtures of hæmolytic sera or mixtures of other indifferent hæmolytic agents—for example, mixtures of saponin and ammonia

—produce a much greater amount of hæmolysis than would correspond to the effects of the separate hæmolytic agents (*Cernovodeanu, Arrhenius*).

In all these cases we are dealing with the combined action of pharmacologically dissimilar substances, for pharmacologically similar substances simply produce the summation of their separate actions.

While *Honigmann's* experiments with mixed narcosis with ether and chloroform or ether and alcohol apparently indicate a potentiation, *Bürgi* and *Madelon* have not been able to confirm his results in experiments which are free from sources of error. However, theoretically such a potentiation could be possible, for *Führer* has shown that the solubility of chloroform in water is diminished by the addition of ether, and consequently the distribution coefficient of such a mixture between water and oil (see p. 105) is altered in such a fashion as to favor an augmentation of its narcotic effects. However, this alteration is so slight in those solutions of the narcotics which actually are formed in the body during anæsthesia, that they are practically of no significance.

It consequently appears as if the function of cells is more markedly and more readily influenced when a smaller number of different constituents of their protoplasm is acted upon chemically or physically than is the case when a larger number of similar constituents are thus acted upon.

Apparently the same holds true for the action of toxic substances on lower organisms. *Lépine* has recommended for parenchymatous disinfection a mixture of several antiseptics in such extreme dilution that no harmful effect either on the tissues treated or on the pathogenic bacteria could be expected. The mixture of these different antiseptics, however, proved to be very efficient antiseptically, but completely harmless for the host, because the larger number of the ingredients were by themselves hardly toxic at all. If the dilutions employed by *Lépine* are noted, it is apparent that the antiseptic effect of the whole mixture cannot be explained as the result of simple addition. However, systematic investigations of such potentialized effects of antiseptic mixture have not yet been conducted.*

More recently such combination methods have been employed by *Ehrlich* in the treatment of trypanosome diseases, he having found that the combination of less active trypan dyes with other less toxic basic dyes formed very effective mixtures, and having obtained similar results with the proper combination of different arsenic compounds.

It may be that the same principle lies at the bottom of the favorable therapeutic effects which the older medicine often endeavored to obtain by the use of mixtures of different drugs. In this connection mention may be made of the practical value of combinations of cathartics. The old experience that opium is distinctly more efficient in quieting the intestine and relieving colic than is accounted for

* The synergism of phenol and the cresols and solutions of salts rests upon a quite different basis, being explainable physically (see p. 504).

by the morphine contained in it, may be explained as resulting from the synergistic action of its various alkaloids.

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Hypersusceptibility.—While in the preceding paragraphs it has been possible to explain at least a portion of the various insusceptibilities as the result of antagonism,—or, more correctly expressed, as the result of the fact that certain chemical substances combine with or destroy each other,—on the other hand, it appears that the explanation for certain types of hypersusceptibility or idiosyncrasy is to be found in the synergistic action of two or more substances. Thus, in accordance with certain observations previously noted, it may be possible to explain the extreme susceptibility of certain individuals to cocaine as due to the fact that in these individuals there is from the start an exaggerated tone of the sympathetic system, which is constantly kept in a state of excitation by epinephrin, so that even the slightest augmentation of this tone produces exaggerated effects.

In a similar fashion *Eppinger* and *Hess* attribute abnormal susceptibility to pilocarpine to an abnormally high vagus tone, which in turn is attributed by them to the action of a vagotonic hormone.

Fröhlich and *Chiari* have shown that the excitability of the vegetative nervous system and of the cerebrospinal nerve-endings is markedly augmented by diminishing the lime content of the body, substances administered to an animal or formed in its own metabolism which deprive the body of lime—*e.g., oxalic acid*—rendering it abnormally susceptible to drugs exerting such pharmacological actions. The same seems also to hold good for many phlogogenetic substances, for, according to *Chiari* and *Januschke,* the degree in which the vessels become permeable and in which transudations occur is dependent on the lime content of the tissues, its augmentation hindering the formation of transudates and œdema while its diminution increases these. The reaction of the skin to phlogogenetic stimuli is also dependent in the same way upon its lime content (see p. 495).

Calcium is, however, not the only constituent of protoplasm the varying amount of which determines or influences its momentary power of reacting to drugs and poisons, but is only a better known and more thoroughly investigated example of the importance of the

composition of the tissue fluids, and one which renders it probable that the remarkable susceptibility of many individuals to certain substances, such as morphine, strawberries, shell-fish, etc., is dependent on a peculiar chemical composition of the tissue fluids and protoplasm.* The old name idiosyncrasy, meaning peculiar mixture, would therefore appear based upon a fundamentally correct idea.

The nature of certain other kinds of hypersusceptibility is still entirely inexplicable, this being particularly the case with acquired cellular hypersusceptibility to certain toxins. If an animal receive small doses of tetanus toxin, which produce almost imperceptible or no toxic effects, its central nervous system becomes hypersusceptible to this toxin, so that amounts thereof which ordinarily would have no effect cause the development of severe tetanus (*v. Behring*).

This hypersusceptibility of the nervous system may be readily demonstrated by the injection of tetanus toxin into the nerve-trunks or the central nervous system of immunized animals, whose blood and other body fluids contain tetanus antitoxin (*Meyer u. Ransom*). It manifests itself even more clearly in animals which have been inoculated intraneurally with a dose of tetanus large enough to cause only a slight local tetanus. In such animals no antitoxin is formed, but, on the contrary, after the lapse of 2 or 3 weeks an extreme hypersusceptibility develops, so that a severe general tetanus results from the subcutaneous injection of amounts of the toxin which ordinarily would produce no tetanus (*Loewi u. Meyer*).

This might all be looked upon as due to the summation of the action of the two doses were it not for the paradoxical fact that two or more very small doses, injected into the spinal cord at long intervals, produce much greater toxic effects than a many times larger dose injected at one time. This might be explained on the assumption, that, when one large dose of the toxin is administered, those tissues which are not specifically susceptible—the connective tissues, etc.—absorb the toxin relatively more rapidly or in larger amounts, in comparison with the nervous protoplasm, than is the case when a small dose is administered, in which latter case the nerves would absorb relatively more of the toxin; in other words, on the assumption that the distribution of the toxin to the different tissues varies greatly with its varying concentration. In a previous section (p. 562) a similar behavior of pharmacological agents has already been instanced. Otherwise there remains only the assumption that the first subliminal poisoning has gradually produced a persistent alteration of the condition of the spinal cord, as a result of which its power of reacting to this toxin has been very gradually augmented,—in other words, the assumption of a sensibilization, a *true cellular hypersusceptibility.*

A certain analogy for this is furnished by the so-called autocatalytic reactions. Catalyzers are substances which accelerate or facilitate certain chemical

* In this connection see *Reid Hunt*, The Effects of a Restricted Diet and of Various Diets on the Resistance of Animals to Certain Poisons, Hyg. Labor. Bull. No. 69, Washington, June, 1910.

reactions. Now, there are certain chemical reactions in which a catalyzer is produced, which accelerates this very same reaction, so that, when it has once started, it progresses with steadily increasing rapidity and intensity, the elements which react with each other being sensibilized to each other. Numerous biochemical processes exhibit this progressive character (*Robertson*).

Behring and *Kitashima* have apparently shown that something of the same kind occurs in rabbits, repeatedly slightly poisoned with diphtheria toxin, in whom hardly any antitoxin is formed.

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ANAPHYLAXIS.—Another type of hypersusceptibility, named by *Richet* "anaphylaxis" (ana—without, phylos—weapon), appears to be of an entirely different nature.

If a foreign proteid substance, either toxic or non-toxic, be subcutaneously or intravenously administered to an animal, after a lapse of some weeks the intravenous injection of a very small amount of this same substance (and this substance only) causes a very rapid, severe, and often fatal poisoning, which in its character is always the same no matter what kind of proteid has been used to sensitize the animal. The symptoms produced vary, however, with the species of animal used, being in the case of dogs those of vascular paralysis, vomiting, purging, dyspnœa, general muscular weakness, and unconsciousness, while in the rabbit they are chiefly due to a peripherally induced spasm of the bronchial muscles which mechanically prevents respiration. Witte's peptone, when injected intravenously, produces the same symptoms in these animals (*Biedl u. Kraus*), so that it may be concluded that the anaphylaxis poison is identical with or similar to some substance present in this mixture.

It would appear that, as a result of the first injection of the antigen, the organism gradually manufactures a specific antibody which, when it again comes into contact with the antigen, forms a substance which is acted upon and decomposed by a peptic ferment present in the blood-plasma, with the formation of the anaphylactic poison which causes the anaphylactic shock. Inasmuch as, if the animal survives this shock, he is immune to this antigen, it would seem that the antibody or the hypothetical ferment in the blood has been entirely consumed in the first anaphylactic reaction. This antibody persists in the blood for a long time, sometimes for many years, and may be transferred to normal individuals if they be transfused with such a

serum, so that they also react to the antigen in question with an acute anaphylactic shock.*

In man such anaphylaxis has been observed particularly in individuals treated with various antitoxic sera, the symptoms consisting of exanthematous eruptions, œdema, fever, general malaise, and collapse. Similar symptoms also occur in specifically susceptible individuals after eating certain foods, among others egg albumen, and in this case, too, the symptoms are to be attributed to an anaphylactic predisposition acquired in some fashion or other (*Bruck, Klausner*). Thus far we have been unable to gain any further insight into the nature of these remarkable phenomena, and still less explained is the hypersusceptibility of the tissues observed in repeated infection with hay-fever toxin, tuberculin, vaccine, and other bacterial toxins (*von Pirquet*). This is also the case with idiosyncrasies to certain chemical well-defined substances, among which special mention should be made of iodoform and antipyrine, which in predisposed individuals regularly cause exanthemata and œdema, with fever, dyspnœa, and pronounced lassitude. *Bruck's* experiments have shown that this predisposition may be induced in animals by the injection of the blood-serum of predisposed individuals, and consequently it too appears to be of an anaphylactic nature (*Klausner*). *Bruck* explains it as follows: Under the chemical influence of these substances a heterologous proteid is formed in the body which acts as an antigen, and when, following the renewed ingestion of the drug, this is again formed, it excites the anaphylactic attack.

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In the discussion of various pharmacological actions, reference has repeatedly been made to the fact that pathological conditions produce alterations in the functions and reactions of the various organs and thus provide altered conditions for pharmacological actions. Our knowledge of pharmacological actions under such conditions must in many cases be based solely upon clinical experience and observation, for, with the exception of certain experimental infections, it is but seldom possible in the laboratory experimentally to produce and analyze disturbances similar to those occurring in human disease. Wherever

* For literature see *Anderson* and *Frost, Biedl. u. Kraus, Pfeiffer, Friedberger.*

it has been possible to do this experimentally, pharmacologists have been able to amplify the fundamental knowledge obtained by experiments on normal animals by that obtained in diseased ones and to note the differences in such actions as observed under pathological conditions. This has been especially the case in the investigation of the antipyretics and of those drugs influencing the circulation, the respiration, the formation of blood, the metabolism, and the processes of inflammation. Such experimental therapy has thus been able to give the explanation for, and the theoretical foundation of, not only etiotropic treatment, but also for the symptomatic treatment of many pathological conditions.

However, in so far as it is not a question of purely etiotropic pharmacological actions, it is always the analytical experiment on normal animals or organs which forms the actual foundation for our pharmacological knowledge and the deductions drawn therefrom. Consequently, it is entirely correct to question whether, and how far, these deductions hold true for pharmacology in its connection with normal, and particularly in connection with diseased, human beings.

Although, with the exception of the cerebrum and the skin, human organs and their reactions do not differ essentially from those of other mammals, and consequently pharmacological laws discovered by experiments on animals may in principle be applied to man, still there are sufficient, although not always clearly understood, reasons why the phenomena observed in pharmacological experiments on animals do not always agree entirely with the therapeutic effects as observed at the bedside. As a matter of fact, it is the outspoken or quietly cherished opinion of many physicians that the effects of drugs in human patients can in no way be reconciled with those observed in animal experiments, and that the latter are, generally speaking, of no value for practical therapeutics, in which experience by the bedside should be the sole guide for the physician.

On the surface this view appears to be correct, for there is no doubt that with the aid of such experiences the physician may be a successful therapeutist, just as an experienced peasant may be a good farmer. It would be unfortunate if neither the cultivation of the ground nor the treatment of the sick were possible without theoretical understanding, for this is neither desired nor possessed by every one. It is also not to be questioned that the practically experienced man possessing no theory would, for the time at least, be a more useful farmer or physician than the theoretical individual who possesses no practical experience. Advances, however (for example, in agriculture the employment of artificial fertilizing agents), are only very exceptionally made without the aid of theoretical knowledge, and for this reason alone, not to speak of others, theoretical knowledge is absolutely indispensable for practical therapeutics. Every apparently erroneous dictum of pharmacology is probably capable of sooner or

later being explained, and if theory is to become a guide for practice it must never disregard those practical experiences which rest on a firm foundation. As a matter of fact, there can be absolutely no contradiction between correct theory and correctly interpreted practical experience. Actually the often proclaimed contradiction between pharmacological theory and clinical experience, as between theory and practice in any case, is due to nothing else than the fact that, from premises gained by experiments, incorrect or too far-reaching deductions are drawn and built up to form an incorrect theory. The apparent discrepancies between theory and practice will always show themselves wherever the adequate and necessary conditions of the experiment are very numerous and only to be learned and controlled gradually. This must be the case particularly often in medicinal therapy, where in most cases the effects observed will not be solely the direct pharmacological action of the drug, but will be the result of many complicating factors.

For example, in the intestine the effect of the pharmacological action of opium may express itself in an evacuation of the bowels after a constipation lasting for many days, or, conversely, by a constipation after a diarrhœa lasting an equal time (see p. 192); or in the kidneys, according to circumstances, the pharmacological action of pilocarpine may result in augmentation or diminution of the kidney secretion (see p. 375).

It is consequently necessarily futile, and therefore unjustifiable, to demand that from pharmacological experiments alone one should deduce and predict the successful action of a drug in each separate pathological condition, for this is just as impossible as it would be to foresee the whole clinical symptom complex, which will result in any given case from a certainly known cause of disease, such as an infection with typhoid; for here, too, in different cases, different secondary conditions result from the primary disturbance, which are dependent on various fortuitous conditions, just as is the case with the symptoms resulting from a pharmacological action. In order to foresee with a certain exactness those symptoms on which will depend the therapeutic effects, it would be necessary that one could correctly judge of the condition of all the organs of the body which may be of importance in a given case. Just here it is that the physician's art, and his intuition, which has been ripened by experience, should play its part in combination with his theoretical knowledge.

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